Archives of Dermatology and Syphilology

VOLUME 42 NOVEMBER 1940 NUMBER 5

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LICHEN SCLEROSUS ET ATROPHICUS

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It is our belief that lichen sclerosus et atrophicus, which has often been designated "lichen planus sclerosus et atrophicus" (Hallopeau [1]), "lichen planus morphoeicus" (Crocker [2]) or "white spot disease" (Johnston and Sherwell [3]) in the German literature, is a distinct entity and can be distinguished both clinically and pathologically from atrophic forms of lichen planus on the one hand and from localized forms of scleroderma, including morphoea guttata, on the other hand. We urge the abandonment of the term "white spot disease," which has been loosely employed in different countries and by different authors to designate both lichen sclerosus [4] and morphoea guttata.[4a]

The present study is based on a review of 46 cases of lichen sclerosus et atrophicus. In 19 the diagnosis was confirmed by removal of a specimen of skin for biopsy. Distinction was made between lichen sclerosus et atrophicus and various forms of localized scleroderma, including morphoea guttata, atrophic forms of lichen planus and kraurosis vulvae. A few cases in which there was insufficient clinical or pathologic data for accurate diagnosis were not included in this series but were considered in regard to differential diagnosis.

From the Section on Dermatology and Syphilology, the Mayo Clinic.

Read at the Sixty-Third Meeting of the American Dermatological Association, Inc., Colorado Springs, Colo., May 31, 1940.

1. Ormsby, O. S.: Diseases of the Skin, ed. 5, Philadelphia, Lea & Febiger, 1937, pp. 311-316.

2. Crocker, cited by Ormsby.[6]

3. Johnston, J. C., and Sherwell, S.: "White-Spot Disease," J. Cutan. Dis. **21**: 302-307 (July) 1903.

4. (*a*) Ehrmann, S., and Brünauer, S. R.: Sclerodermie, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 8, pt. 2, pp. 763-773. (*b*) Miescher, G.: Weissfleckenkrankheit (Lichen sclerosus—White spot disease—kartenblattähnliche Sklerodermie), Arch. f. Dermat. u. Syph. **172**:419-429, 1935. (*c*) Johnston and Sherwell.[3]

LITERATURE

Before giving the clinical and pathologic observations in our cases, a brief review of the literature is necessary, because of the confusion in terminology which exists. This confusion probably has resulted, first, because of the close similarity of the cutaneous pictures of lichen sclerosus et atrophicus and some examples of morphoea guttata and, secondly, because a histologic picture for lichen sclerosus et atrophicus distinct from that of morphea and from that of atrophic lichen planus has not generally been recognized. However, on the basis of a study of our cases we believe that such a picture does exist. In this country, since the appearance of the articles of Montgomery and Ormsby,[5] Ormsby,[6] MacKee and Wise [7] and Wise and Rosen,[8] the term "white spot disease" has been confined to localized forms of scleroderma, including morphoea guttata or lichenoid scleroderma. The authors just mentioned clearly distinguished lichen sclerosus and morphoea guttata. In the French literature Petges [9] spoke of *morphée en gouttes* as being related to card-like scleroderma, yet the features in his case, especially the pathologic features, are those of lichen sclerosus et atrophicus. In this paper the term morphea, or morphoea guttata, is used in the sense of localized scleroderma.

Hallopeau [10] in various reports of cases used the terms "lichen planus atrophic," "lichen planus sclerosus" and "lichen planus sclerosus of Wilson." Darier [11] emphasized the cardinal histologic features of lichen sclerosus et atrophicus but compared them to those of lichen planus in which the characteristic infiltrate in the upper portion of the cutis seen in lichen planus has been replaced by an area of sclerosis. Unna's

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5. Montgomery, F. H., and Ormsby, O. S.: White Spot Disease (Morphoea Guttata) and Lichen Planus Sclerosus et Atrophicus: A Clinical and Histological Study of Three Cases, with a Review of the Literature, J. Cutan. Dis. **25**:1-16, 1907.

6. Ormsby, O. S.: Lichen Planus Sclerosus et Atrophicus (Hallopeau): A Report of Six Cases (Five New) with a Review of the Literature, J. A. M. A. **55**:901-907 (Sept. 10) 1910.

7. MacKee, G. M., and Wise, F.: White Spot Disease, J. Cutan. Dis. **32**:629-660 (Sept.) 1914.

8. Wise, F., and Rosen, I.: Further Observations on So-Called White Spot Disease or Sclerodermia Circumscripta, J. Cutan. Dis. **35**:66-89 (Feb.) 1917.

9. Petges, G.: La morphée en gouttes et le white-spot disease, Ann. de dermat. et syph. **44**:415-437, 1913.

10. Hallopeau, H.: (*a*) Lichen plan scléreux, Ann. de dermat. et syph. **20**:447-449 (March) 1889; (*b*) Sur un nouveau cas de lichen plan atrophique, ibid. **27**: 57-60 (Jan.) 1896; (*c*) Sur un nouveau cas de lichen de Wilson scléreux, ibid. **29**: 358-360 (April) 1898.

11. Darier, J.: Lichen plan scléreux, Ann. de dermat. et syph. **23**:833-837 (July) 1892.

pathologic description of cardlike scleroderma [12] approximates that of lichen sclerosus and is not that of morphea or other forms of localized scleroderma. This was recognized by Kyrle,[13] who, however, would liken the pathologic picture to that of acrodermatitis chronica atrophicans. Cardlike scleroderma of Unna, therefore, probably is lichen sclerosus et atrophicus, and Miescher has so classified it; but again, the term has been misused in some instances to include morphea. The earlier literature has been reviewed in detail in articles by Montgomery and Ormsby,[5] Ormsby,[6] MacKee and Wise [7] and Wise and Rosen.[8] It is difficult accurately to classify many of the cases in the older reports because of inadequate clinical or pathologic data. Westberg's [14] case, on the basis of his illustrations, is an instance of morphea. Johnston and Sherwell's [3] case of white spot disease suggests clinically and is typically one of lichen sclerosus et atrophicus on the basis of pathologic descriptions and illustrations, and the same is true of Hazen's case. Hazen [15] stated the opinion that the lesions in his case started as morphoea guttata and changed to lichen sclerosus. He offered no proof, however, that the earlier lesions in his case might not have been those of an edematous stage of lichen sclerosus et atrophicus. This case (Hazen's) has been cited as an example of transitions between morphea, cardlike scleroderma of Unna, white spot disease and lichen sclerosus et atrophicus. It is our belief that most of the eruptions can be accurately classified and that they do not represent the merging of two or more conditions.

There are many cases reported in the literature as lichen sclerosus et atrophicus which clinically and histologically were merely atrophic forms of lichen planus.[16] This type is designated in the German literature as a "secondary type of lichen sclerosus." Many authors, however, still regard lichen sclerosus et atrophicus as a form of atrophic lichen planus.[17]

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12. Unna, P. G.: The Histopathology of the Diseases of the Skin, translated by N. Walker, Edinburgh, William F. Clay, 1896.

13. Kyrle, J.: Histobiologie der menschlichen Haut und ihrer Erkrankungen, Berlin, Julius Springer, 1925, vol. 1, pp. 140-141.

14. Westberg, F.: Ein Fall von mit weissen Flecken einhergehender, bisher nicht bekannter Dermatose, Monatsh. f. prakt. Dermat. **33**:355-361 (Oct. 1) 1901.

15. Hazen, H. H.: An Anomalous Case of White-Spot Disease, J. A. M. A. **61**: 393-396 (Aug. 9) 1913.

16. Vignolo-Lutati, K.: Ueber den sogenannten Lichen albus von Zumbusch, Dermat. Wchnschr. **54**:661-677, 1912. MacKee and Wise.[7]

17. (*a*) Juliusberg, F.: Lichen ruber und Pityriasis rubra pilaris, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 7, pt. 2, pp. 1-221. (*b*) Montgomery, D. W., and Culver, G. D.: Lichen Sclerosus Vulvae, J. Cutan. Dis. **33**:572-578 (Aug.) 1915. (*c*) Pautrier, L. M.: Lichen plan atrophique ou scléreux, in Darier, J., and others: Nouvelle pratique dermatologique, Paris, Masson & Cie, 1936, vol. 7, pp. 490-492. (*d*) Schubert, M.: Zur Kenntnis des Lichen sclerosus atrophicans (Weissfleckenkrankheit), Dermat. Wchnschr. **103**:1653-1662 (Dec. 19) 1936.

Eruptions that possibly were lichen sclerosus et atrophicus have been described in the older literature under a multiplicity of names, only two of which need be mentioned. Lichen albus of von Zumbusch [18] and chronic atrophic lichenoid dermatitis of Csillag [19] have been classified with lichen sclerosus et atrophicus by many authors, including Ormbsy, Nomland [20] and Hallopeau, are grouped with morphoea guttata and lichenoid scleroderma by some authors [21] or are considered to be separate entities by others.[22] On the basis of a careful review of the original cases reported by von Zumbusch and Csillag, we believe that these conditions are simply variants or types of lichen sclerosus and that, whereas there is some clinical similarity between Csillag's case and the case reported by Wise and Shelmire of chronic atrophic lichenoid dermatitis, the pathologic features are entirely different in the 2 cases. Wise and Shelmire,[21] we believe, were correct in regarding the histologic changes in their case as those of scleroderma, and their case might perhaps be better designated as one of "diffuse generalized lichenoid scleroderma."

There is no further need to discuss older cases in the literature in which the eruptions have been classified differently by various authors.[23] Wise and Ormsby and others [24] limited the term "white spot disease" to morphoea guttata, which distinction, however, has not been accepted in the foreign literature.[25] Miescher [4b] in a recent article spoke of lichen sclerosus as "white spot disease" or "cardlike scleroderma," but, together with Schubert,[17d] Kwiatkowski,[26] Kogoj [27] and also Nomland,[20] he

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18. von Zumbusch, L. R.: Ueber Lichen albus, eine bisher umbeschriebene Erkrankung, Arch. f. Dermat. u. Syph. **82**:339-349, 1906.

19. Csillag, J.: Dermatitis lichenoides chronica atrophicans (Lichen albus v. Zumbusch), in Neisser, A., and Jacobi, E.: Ikonographia dermatologica, Berlin, Urban & Schwarzenberg, 1909, pp. 147-151.

20. Nomland, R.: Lichen Sclerosus et atrophicus (Hallopeau) and Related Cutaneous Atrophies, Arch. Dermat. & Syph. **21**:575-594 (April) 1930.

21. Wise, F., and Shelmire, B.: Chronic Atrophic Lichenoid Dermatitis (Csillag): So-Called Lichen Albus of Zumbusch, Arch. Dermat. & Syph. **18**:179-199 (Aug.) 1928.

22. (*a*) Hoffman, E.: Ueber einen mehrere Jahre hindurch beobachteten Fall von Lichen sclerosus, in Neisser, A., and Jacobi, E.: Ikonographia dermatologica, Berlin, Urban & Schwarzenberg, 1909, pp. 153-157. (*b*) Wise and Shelmire.[21]

23. Miescher.[4b] Ormsby.[6] Petges.[9]

24. Bunch, J. L.: Morphoea Guttata, Brit. J. Dermat. **27**:77-85 (March) 1915.

25. Petges, G., and Petges, A.: White Spot Disease, in Darier, J., and others: Nouvelle pratique dermatologique, Paris, Masson & Cie, 1936, vol. 6, pp. 179-194. Ehrmann and Brünauer.[4a]

26. Kwiatkowski, S. L.: Lichen sclerosus, Arch. f. Dermat. u. Syph. **172**:395-408, 1935.

27. Kogoj, F.: (*a*) Lichen sclerosus (atrophicus) primitivus, Arch. f. Dermat. u. Syph. **169**:465-469, 1934; (*b*) Ueber die Stellung des Lichen sclerosus im System, ibid. **173**:615-623, 1936.

regarded lichen sclerosus as a disease entity. Grzybowski [28] stated that in his opinion lichen sclerosus is not an independent disease, and he referred to the histologic resemblance of lichen sclerosus to true lichen planus. His illustrations, however, appear to be those of lichen sclerosus et atrophicus. Wise and Sulzberger [29] stated that lichen sclerosus is a form of lichen planus. Feldman [30] would call attention to lichen planus acuminatus atrophicans and to the fact that folliculitis decalvans and lichen spinulosus of Little probably are a follicular form of lichen planus and that lichen sclerosus of Hallopeau is lichen planus. In the cases which he reported the conditions probably are forms of lichen planus and histologically do not show features of lichen sclerosus except for the follicular keratotic plugs. Finally, we must refer to the article by Hunt,[31] who described a series of cases of leukoplakia, kraurosis and lichen planus of the vulva and who, we believe, confused the picture of kraurosis vulvae with that of lichen sclerosus et atrophicus of the vulva because of the similarity of histologic changes in the two conditions, although the clinical appearance of each condition is distinctive. Ketron and Ellis [32] also have apparently confused kraurosis and leukoplakia with lichen sclerosis.

That the entire subject of lichen sclerosus, atrophic forms of lichen planus, morphea and kraurosis even today is viewed differently by leading dermatologists is evidenced by the discussion of a group of cases of circumscribed scleroderma or leukoplakia of the vulva, circumscribed white spot disease, kraurosis vulvae and white spot scleroderma and circumscribed scleroderma presented at the Atlantic Dermatologic Conference in December 1938,[32b] in which different opinions were expressed

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28. Grzybowski, M.: Ueber den sogenannten Lichen sclerosus, Arch. f. Dermat. u. Syph. **175**:222-231, 1937.

29. Wise, F., and Sulzberger, M. B.: Editorial Comment, in Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1937, p. 236.

30. Feldman, S.: (*a*) Lichen Planus et Acuminatus Atrophicans: Lichen Plan Atrophicus, Lichen Plan Scléreux, Hallopeau; Lichen Ruber Planus Keloidiformis, Pawlow; Lichen Planus Morphoeicus, Crocker; Lichen Albus, Zumbusch, Arch. Dermat. & Syph. **5**:102-113 (Jan.) 1922; (*b*) Lichen Planus et Acuminatus Atrophicans: Folliculitis Decalvans et Lichen Spinulosus of Little, ibid. **34**:378-397 (Sept.) 1936.

31. Hunt, E.: Leukoplakia Vulvae, Kraurosis Vulvae, and Lichen Planus of the Vulva, Brit. J. Dermat. **48**:53-84 (Feb.) 1936.

32. (*a*) Ketron, L. W., and Ellis, F. A.: Kraurosis Vulvae (Leucoplacia) and Scleroderma Circumscripta: A Comparative Histological Study, Surg., Gynec. & Obst. **61**:635-650 (Nov.) 1935. (*b*) Ginsberg, L.: Circumscribed Scleroderma or Leukoplakia of the Vulva in a Child Aged Eight Years, Arch. Dermat. & Syph. **39**:903 (May) 1939; Circumscribed Scleroderma (White Spot Disease) Leukoplakia of the Vulva, ibid. **39**:903 (May) 1939. Ketron, L. W., and Ellis, F. A.: Kraurosis Vulvae and White Spot Scleroderma, ibid. **39**:904 (May) 1939. Bernstein, J. C., and Robinson, H. M.: Circumscribed Scleroderma, ibid. **39**:904 (May) 1939.

by Ketron, Wise, Stokes, McCarthy, Ellis, Goodman and Bernstein. McCarthy even stated that in lichen sclerosus et atrophicus evidence of true lichen planus will always be found if enough sections are cut.

CLINICAL FEATURES

Excellent clinical descriptions of lichen sclerosus et atrophicus are given by Ormsby,[1] Nomland, Miescher and others.[33] Ormsby [1] stated:

> The characteristic lesion . . . is an irregular, often polygonal, flat-topped, white papule. The white color of the lesions is striking, and has been compared with that of ivory and mother-of-pearl. The papules, as a rule, are firm to the

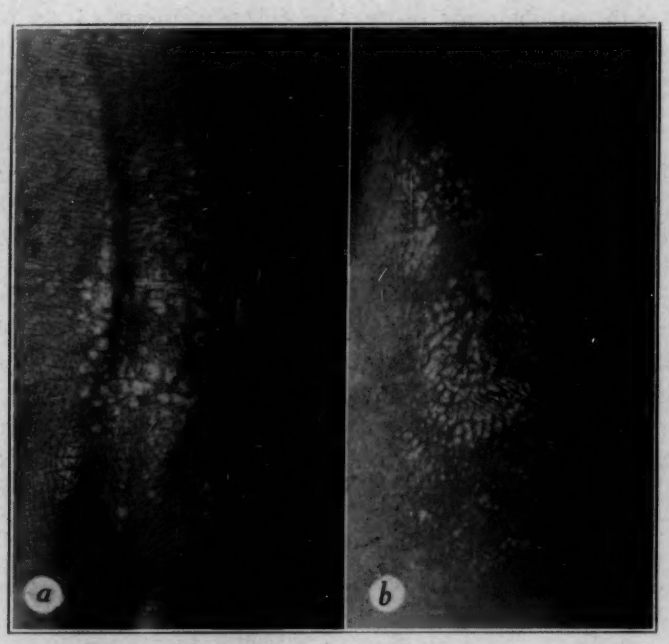

Fig. 1.—Lichen sclerosus et atrophicus. Typical polygonal whitish papule with central dells and plugs of fifteen months' duration on (*a*) the hand and (*b*) the neck of a woman aged 27. Histologic changes also were present.

touch, neither elevated nor depressed, but slight elevation may be present. Generally, no areola is present, but at times a rosy or moderately pigmented zone may surround the papules. These may be discrete or grouped, and in most cases present both types. When grouped to form plaques, the outline of the individual papules forming the plaques can be determined. Each papule has on its shining, smooth surface from one to several black or dark, horny, comedo-like plugs, or minute bead-like depressions, which show the former sites of horny plugs. These elements are situated at the pilosebaceous or sweat-pore orifices, and are important from the view-point of diagnosis.

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33. Schamberg, J. F., and Hirschler, R.: Lichen Planus Sclerosus, with Report of a Case, J. A. M. A. **53**:369-373 (July 31) 1909. Hoffman.[22a]

When atrophy occurs in the later stages the keratotic plugs or central delling becomes more prominent. At times, however, and especially in the early stages of the disease, keratotic plugs or depressions may not be recognized clinically but are almost invariably present on pathologic examination. (For varied clinical features see figures 1,

Fig. 2.—Lichen sclerosus et atrophicus, with rather unusually infiltrated plaques on (*a*) both wrists and (*b*) both knees, and with partial involution of plaque over (*c*) the sacrum. Lesions also were present on the back and the neck. These lesions were of four years' duration in a woman aged 60. (For typical histologic changes see figure 6 *a*.)

2, 3 and 4.) In the stages of involution a white parchment-like or tissue-paper-like wrinkling simulating that seen in atrophic forms of morphoea guttata is seen.

The salient observations in our series of 46 cases are given in the table. The disease was about six times as frequent among women as

among men. In only 8 of the 46 cases did the condition occur in men. The ages of the patients at onset of the disease varied from 10 years to 61, but the average age of the men at onset was 43, as calculated from the ages of the 8 men, and that of the women 50, as calculated from the ages of the 38 women, in the present series. The sites of predilection of the disease are the upper portions of the trunk, the neck, the axillas and the forearms, but apparently the disease can start anywhere on the body, from the neck down. In differential diagnosis in regard to kraurosis vulvae, in 6 of our cases of lichen sclerosus the lesions were limited to the vulva and anus, and in 20 of our cases there was definite involvement of the vulva as well as of other parts of the body. In many

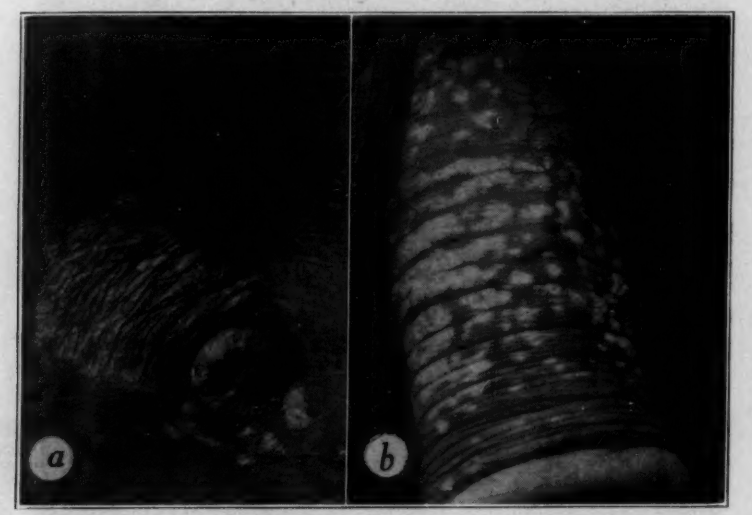

Fig. 3.—Lichen sclerosus et atrophicus; typical lesions (*a*) about the umbilicus and (*b*) on the penis, of two years' duration, occurring in a man aged 37. When this patient was seen sixteen years later the lesions had undergone complete involution.

instances there was unilateral asymmetric onset. The lesions subsequently became symmetric. Lesions developed elsewhere on the body in some cases only after a period of years. None of our patients showed involvement of the mucous membranes of the mouth, as in a case reported by Hallopeau. There were as many cases in which plaques were present as there were cases in which a lesion, or lesions, consisted chiefly of discrete papules. In 2 cases there were infiltrative plaques suggestive of localized scleroderma, in addition to typical lesions of lichen sclerosus et atrophicus. Specimens for biopsy unfortunately were not taken from these regions. In 1 case, however, there were multiple infiltrated plaques simulating those of an edematous stage of morphea but with characteristic

keratotic plugs clinically and histologically (fig. 2). A moderate degree of pruritus occurred in only about half of the cases, whether generalized or localized, as in cases in which pruritus was limited to the vulva and anus. As a rule, subjective symptoms were minimal. Generally speaking, there were no significant observations on general examination, nor was any etiologic relation to any systemic disease demonstrable. Twenty of the women had reached the menopause when seen at the clinic, but the

Fig. 4.—Lichen sclerosus et atrophicus; typical involvement of labia and perianal region, with characteristic delling and plugging, in a woman aged 65. These lesions were of four years' duration. The diagnosis was confirmed histologically. There were no lesions elsewhere on body.

menopause seemed to bear no relation to the disease, as Monacelli [34] emphasized. A nervous factor was prominent in only 1 of our cases, contrary to the statements in the literature. Results of laboratory studies all were essentially negative. Local treatment, including roentgen

34. Monacelli, M.: Su alcuni casi del cosi detto lichen sclerosus e sui rapporti di questo con gli stati craurotici della vulva, Gior. ital. di dermat. e sif. **75**:1419-1445 (Aug.) 1934.

therapy, and the administration of thyroid extract were without benefit. One patient received benefit from the use of estrone (theelin) plus vitamins. Once the lesions develop, they usually persist, relatively

Clinical Features of Forty-Six Patients Who Had Lichen Sclerosus et Atrophicus

Age	Sex	Duration	Distribution		Histologic Aspects
			Primary Site	Secondary Site	
11	F	1 yr.	Vulva, labia majora		
27	F	15 mo.	Forearm, dorsum of hand	Neck: sides and nape	Typical
28	F	?	Left scapula		Typical
34	F	5 yr.	Back		
36	F	21 yr.	Left shoulder		Typical
41	F	6 mo.	Wrists	Right shoulder	Typical
43	F	1 yr.	Right thigh		
44	F	12 yr.	Abdominal scar	Breasts, vulva	Typical
44	F	2 mo.	?	Wrists, forearm, neck, left thigh, perineum	
45	F	14 mo.	?	Back, hip, arm, feet	
45	F	Months	Vulva, anus	Neck, right shoulder, thigh	Typical
46	F	7 mo.	?	Legs, thighs, vulva, wrists, waist, neck	
48	F	8 mo.	Left breast	Right breast, abdomen	
49	F	1 yr.	Left scapula	Nape of neck, vulva	
49	F	1 yr.	Vulva.	Shoulders, nape of neck	
51	F	?	Perineum, thighs		
52	F	2 yr.	Vulva, anus		
52	F	2 yr.	?	Vulva, anus, sides of neck	
53	F	3 yr.	Left thigh	Right shoulder, axilla, groin, waist	Typical
54	F	30 yr.	Vulva	Anus	Typical
55	F	6 yr.	Wrist, right forearm	Left side of neck, legs	
56	F	30 yr.	?	Neck, arms, breast	
56	F	9 mo.	Ankles	Neck, chest	
56	F	14 mo.	Left leg	Flexors, antecubital and popliteal spaces, axilla, groin, chest	
56	F	?	Wrists		Typical
57	F	6 yr.	?	Right breast, inner aspect of thighs	Typical
57	F	2 yr.	Vulva		Typical
59	F	7 yr.	Vulva		
60	F	1 yr.	?	Left axilla, antecubital space, shoulders	Typical
60	F	4 yr.	Left knee	Right knee, back, sides of neck; dorsa of hands	Typical
60	F	4 yr.	?	Vulva, neck, chest, back,	Typical
62	F	8½ yr.	Wrists	Axilla, vulva	
63	F	1 yr.	Left scapula		
65	F	8 yr.	Breasts, perineum	Back, hips, antecubital and popliteal spaces, clavicles	
65	F	4 yr.	Vulva, anus	Thighs	Typical
65	F	8 yr.	Vulva, anus		
66	F	25 yr.	?	Wrists, legs, perineum	
71	F	Months	Left shoulder	Right shoulder	
28	M	18 mo.	Elbows	Neck, shoulders, thighs, back, abdomen	Typical
37	M	2 yr.	Right hip	Left hip, penis, umbilicus	
39	M	6 mo.	?	Neck, back, forearm, thighs	
42	M	20 yr.	Trunk		Atypical
45	M	8 yr.	Right shoulder	Umbilicus, forearm, trunk (front and back)	
47	M	Years	Wrists, right forearm	Vulva, legs, left side of neck	Typical
50	M	30 yr.	Penis	Umbilicus	
54	M	5 yr.	Back		Typical

unchanged, often for many years. At times spontaneous involution occurred, but at a later date new lesions developed. One patient who clinically had a typically rather extensive example of the condition reported that the lesions disappeared in a few months and that they had

not recurred fourteen years later. This case is an exception to the rule, as is also 1 case reported in the literature.[33]

HISTOLOGIC ASPECTS

Darier tried to reconcile the pathologic process in Hallopeau's first case to the histologic picture seen in ordinary lichen planus. He assumed that the original infiltrate characteristic of lichen planus had disappeared, leaving behind sclerosis and atrophy. Excellent histologic descriptions of lichen sclerosus et atrophicus are given by Darier, Nomland, Miescher and many other authors,[35] but it is in the interpretation of the pathologic changes that we wish to differ.

The first change observed in the earliest lesions consists of an edema beneath the epidermis, with resultant flattening of the rete ridges and papillary bodies and separation of elastic tissue from the papillary bodies in the epidermis. There may or may not be a mild to dense degree of perivascular infiltrate composed chiefly of lymphocytes beneath this area. In a fully developed lesion the zone of edema becomes more pronounced, even to the extent of formation of lacunas beneath the epidermis; this may result from lymphedema, or it may represent dilatation of lymphatic vessels and capillary vessels in the upper part of the cutis. Later, a perivascular infiltrate of varying degree is seen in the midcutis beneath the area of edema, at times assuming a bandlike formation. The epidermis shows pressure atrophy, but with relative and absolute hyperkeratosis and keratotic plugging in relation to the orifices of the dermal appendages and hair follicles and also in relation to the sweat ducts and independently of either (figs. 5, 6 and 7). A moderate degree of intracellular edema of basal and prickle cells and slight liquefaction degeneration or even necrosis of the basal cell layer is seen —the result of lymphedema. At the edge of a papule the infiltrate occasionally may extend up to the epidermis and participate in the liquefaction necrosis, thus suggesting the histologic picture of lichen planus. There is little infiltrate to be seen elsewhere in relation to the epidermis. The infiltrate in the deeper portions of the cutis is composed of a few lymphocytes, plasma cells and mast cells. There is an infiltrate of varying degree about the dermal appendages. The cutaneous nerve bundles occasionally are invaded by the infiltrate. In some cases remnants of elastic tissue fibers can be seen just beneath the epidermis, and in other cases a definite pattern of elastic fibers as seen in the papillary bodies is to be found beneath the area of edema and is simply indicative that

35. Gans, O.: Histologie der Hautkrankheiten, Berlin, Julius Springer, 1925, vol. 1, pp. 306-309. Ehrmann and Brünauer.[4a] Kwiatkowski.[26] Kogoj.[27]

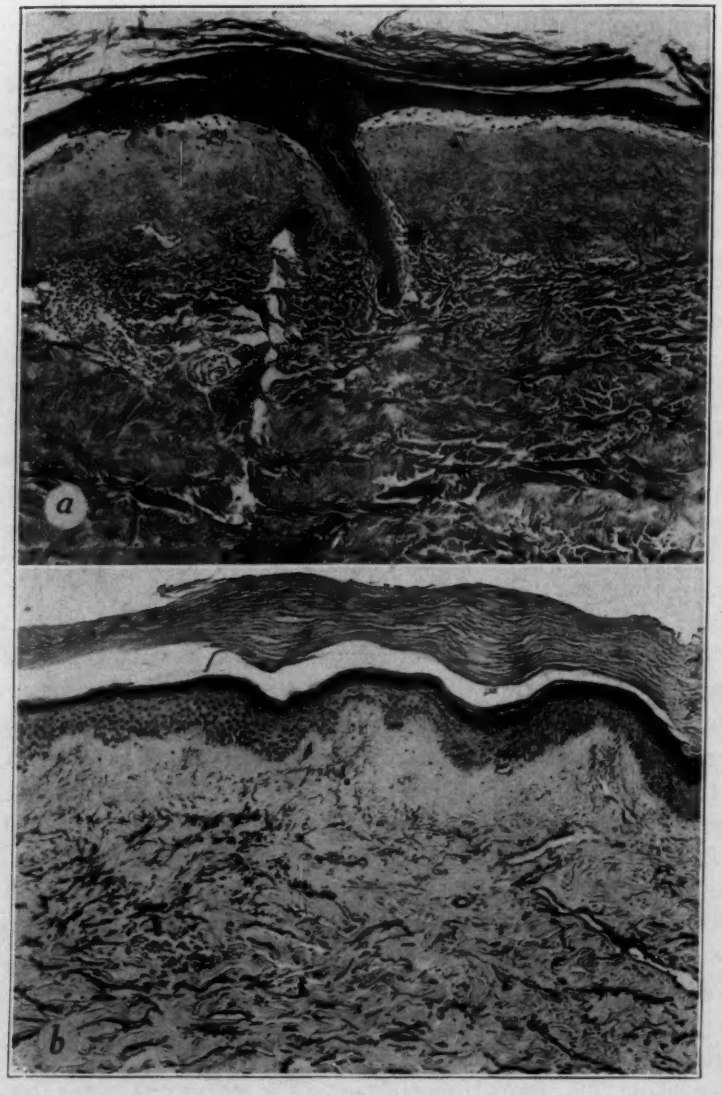

Fig. 5.—Lichen sclerosus et atrophicus. *a*, section from the shoulder (hematoxylin and eosin stain; × 60); note the hyperkeratosis, keratotic plugging in relation to the sweat duct, mild liquefaction necrosis of basal cell layer, dilated lymphatic vessels, homogenization of connective tissue in the upper portion of the cutis and infiltrate in the midcutis. *b*, section of lesion from the wrist; disease of five months' duration (elastin H stain; × 70). This section is from an early papule, showing edema situated just beneath the epidermis and separation of elastic tissue from the epidermis but no destruction of the epidermis.

the elastic tissue has been separated from the epidermis by this area of edema and not that there has been any appreciable destruction of elastic fibers. In the midcutis there would in some cases even appear to be an

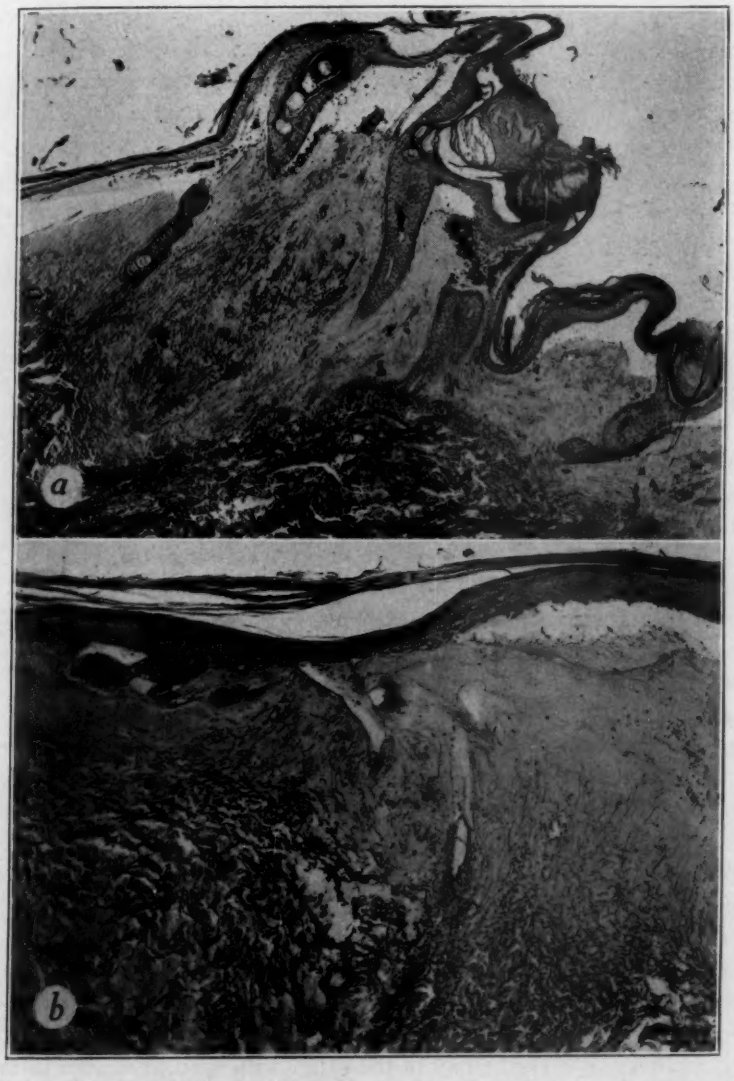

Fig. 6.—Lichen sclerosus et atrophicus. *a*, section of lesion from the back (elastin H stain; × 36), showing extreme grade of keratotic plugging, atrophy of the rest of the epidermis, decided lymphedema, extravasation of erythrocytes, homogenization and edema of connective tissue in the upper portion of the cutis and preservation of elastic fibers staining black. *b*, typical section of lesion from the axilla (elastin H stain; × 60). Note the preservation of fibrils of elastic tissue of papillary bodies reaching up into the regions of edema.

increase in elastic tissue fibers (fig. 6*a*). The edema may be so great as to result clinically in the formation of small vesicles, such cases having been reported in the literature.[36]

The region of edema that occurs beneath the epidermis contains swollen and homogeneous collagen fibers containing very few nuclei. These fibers appear as fine edematous wavy fibrils of collagen often paralleling the epidermis in contrast to their usual longitudinal arrangement in relation to the papillary bodies, which have been flattened and obliterated as the result of lymphedema. These swollen collagen fibers stain poorly with ordinary connective tissue stains. This condition is what has been spoken of as being "sclerosis." We believe, however, that the more logical explanation is that collagen appears to be increased as the result of lymphedema, and that therefore the fibrils have become separated from one another. We believe that this increase in connective tissue is false rather than true, especially since there is no evidence of increase in fibroblasts or connective tissue cells in this region in any stage of the process.

With the use of the Bielschowsky stain, in only 2 of the 19 cases of lichen sclerosus et atrophicus in which specimens for biopsy were obtained was there evidence of increase in *Gitterfasern,* lattice or reticulum fibers, these being regarded by some pathologists as fibers of young connective tissue or of collagen. Results of staining for mucin in the cutis in all but 1 case were negative except for deposits at the orifices of the sweat ducts in the stratum corneum in several cases. In the deeper layers of the cutis a slight increase in fibroblasts and connective tissue occasionally may be seen, but without true sclerosis.

Pigmentation in the epidermis over the area of edema or at the margins, as shown with silver nitrate stain, was normal in some cases, not increased in any cases and often decreased or absent. Staining for hemosiderin gave negative results. The dermal appendages revealed mild to moderate degrees of atrophic changes, which probably were the result of pressure from edema or the result of the keratotic plugging of their orifices.

In stages of involution edema is less pronounced, and the infiltrate beneath the region of edema may become minimal. We have mentioned that there is dilatation of lymph spaces and vessels and at times of capillaries in the upper part of the cutis, and there may at times be slight proliferation of the epithelium of the capillaries, such as is seen in many chronic dermatoses, including eczema. There are, however, no obliterative changes to be found in the larger blood vessels in the deeper portions of the cutis.

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36. Myers, W. K.: Lichen Sclerosus: Case Report, Brit. J. Dermat. **48**:658-660 (Dec.) 1936. Schubert.[17d]

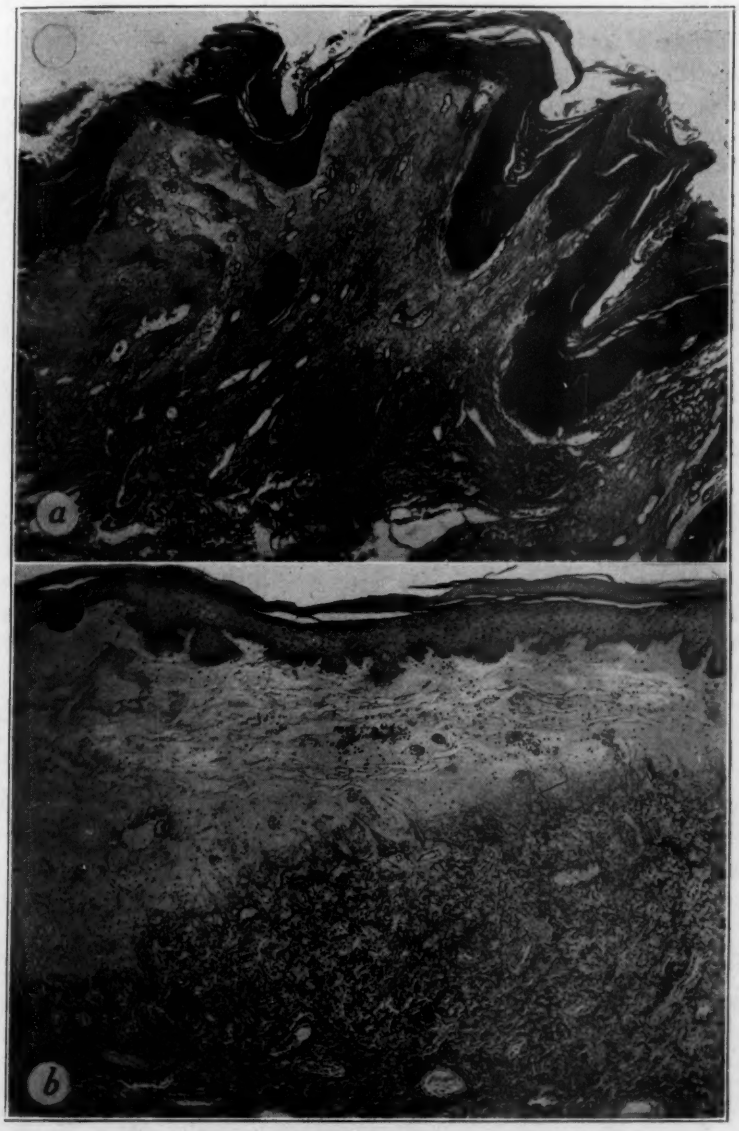

Fig. 7.—Lichen sclerosus et atrophicus. *a*, section of lesion of vulva of thirty years' duration (hematoxylin and eosin stain; × 30), showing typical changes, including hyperkeratosis. Note the acanthosis and pronounced dilatation of the capillaries, possibly the result of previous roentgen therapy. *b*, kraurosis vulvae, showing histologic changes similar to those of lichen sclerosus et atrophicus, but without keratotic plugging and with proliferative changes in the walls of the deeper blood vessels (elastin H stain; × 45).

Most of the changes that we have described are clearly shown in articles by Nomland and by Miescher, as well as in schematic drawings in older articles in the literature. In 18 of our 19 cases there were pathologic features as given and as shown in the photomicrographs, the histologic picture being surprisingly constant, despite the age of the patient or the situation of the lesion from which the biopsy specimen was taken. In 1 case, in which the sections were taken from an old lesion, there was evidence of fibrosis or, essentially, scar tissue, such as might be encountered in many cases of various dermatoses in which the specimen for biopsy is taken from a lesion which had undergone involution. In another case there were early obliterative changes in some of the blood vessels, but this could be attributed to the roentgen therapy that the patient had received previously.

The characteristic histologic changes of lichen sclerosus consist of relative and absolute hyperkeratosis, with keratotic plugging of the hair follicles and dermal appendages and also, independent of either, atrophy of the rest of the epidermis, flattening and loss of the rete ridges, mild liquefaction degeneration or necrosis of the basal layer, which is the result of dilatation of the lymphatic spaces and vessels, lymphedema in the upper portion of the cutis, homogenization and edematous changes in the connective tissue fibers beneath the epidermis, separation of elastic tissue fibers from the epidermis, but without their destruction, an infiltrate in the midcutis beneath the area of edema and absence of obliterative changes in the deeper blood vessels. The histologic picture, therefore, of lichen sclerosus is not that of true sclerosis but is more that of edema and homogenization of the connective tissue. There are no obliterative changes in the deeper blood vessels, which constitute one feature of the characteristics of any type of scleroderma, including morphea.

DIFFERENTIAL DIAGNOSIS

In distinguishing lichen sclerosus et atrophicus from dermatoses with which it might be confused clinically or histologically, the emphasis is placed first on the histologic differentiation, which is of greatest value, especially when the clinical diagnosis is in doubt (with the exception of kraurosis vulvae).

Morphoea Guttata.—The histologic changes occurring in morphea (fig. 8) are wholly different from those of lichen sclerosus et atrophicus. In morphea there is true sclerosis with increase of connective tissue fibers; the infiltrate extends deep into the subcutaneous tissues; decided atrophic changes are seen in the dermal appendages, and there are obliterative changes in the deeper blood vessels. In the late stages the epidermis may be thin and atrophic, with partial loss of rete ridges. Occasionally, some dilatation of lymph spaces or lymph vessels may be

seen just beneath the epidermis. In a large series of cases of morphea, including many of morphoea guttata, studied pathologically at the clinic we have failed to see keratotic plugging, such as is constantly seen in lichen sclerosus. Some of the conditions reported in the older litera-

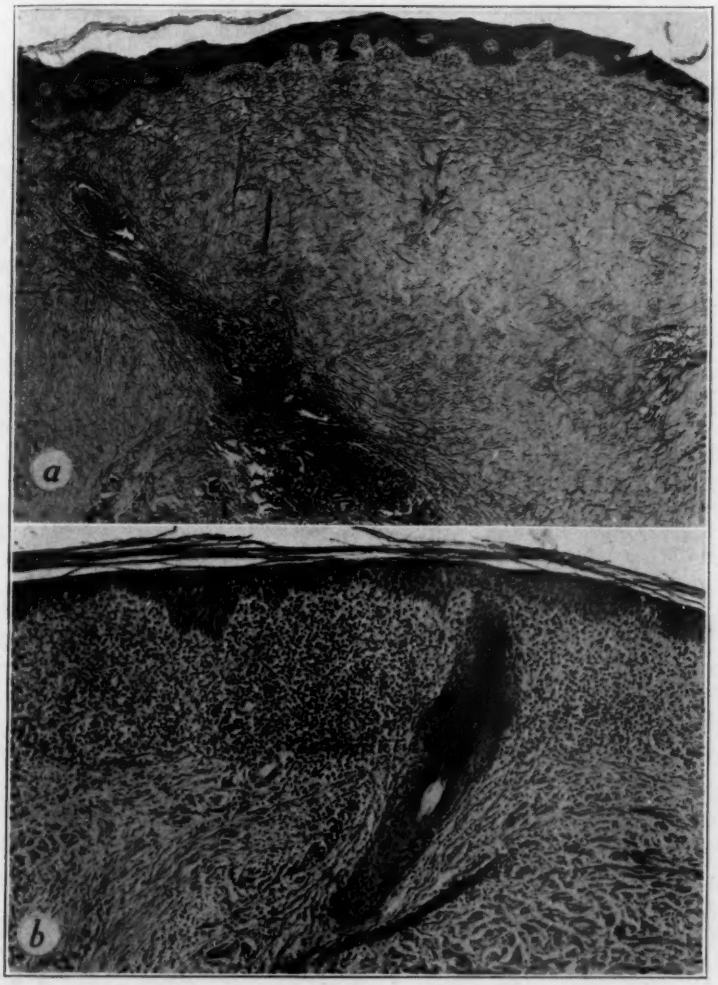

Fig. 8.—*a*, morphoea guttata (hematoxylin and eosin stain; × 35). Some atrophy of the epidermis is present, but the rete ridges are still preserved. There are marked homogenization, increase and sclerosis of connective tissue throughout the cutis, atrophy of the dermal appendages and dense perivascular infiltrate at the edge of the lesion, with obliterative changes in the deeper blood vessels. *b*, atrophic lichen planus (hematoxylin and eosin stain; × 30), showing marked persistent atrophic changes in the epidermis, with liquefaction necrosis and dense infiltrate limited to the upper portions of the cutis.

ture as morphoea guttata with keratotic plugs we believe on analysis were probably lichen sclerosus et atrophicus in which the pathologic picture was misinterpreted as one of true sclerosis and in which the pathologic changes actually were those of lichen sclerosus.

Crocker's term of "lichen planus morphoeicus" for lichen sclerosus et atrophicus emphasizes the close clinical similarity of some instances of morphoea guttata to lichen sclerosus. Figure 9 is an example of such a condition, in which the pathologic picture, however, showed all the features of morphea and none of the features of lichen sclerosus. In most instances morphoea guttata will reveal one or more larger deeply indurated plaques of localized scleroderma. It has been our experience and the experience of O'Leary [37] that in many instances of localized scleroderma, including those of morphoea guttata, the condition undergoes spontaneous involution in a few years. This is the exception in instances of lichen sclerosus et atrophicus. An illustrative case of morphea follows.

For the last ten years we have had under observation a woman who has had extensive generalized morphea. All the larger and typical plaques of localized scleroderma (morphea) have cleared up (at the time of writing). At present the patient has an area on the upper part of the back, just beneath the neck, composed of discrete white indurated papules, 1 to 3 mm. in diameter, without a violaceous border, which photographically could be easily mistaken for lesions of lichen sclerosus atrophicus. There are no keratotic plugs or central delling, and the individual papules are oval rather than polygonal in shape and are definitely indurated on palpation. Lower down on the back is another larger area or plaque, again composed of discrete lesions, 2 to 3 mm. in diameter, in which involution with atrophy has occurred. Some of these lesions now have assumed a polygonal shape and have a white tissue-paper-like surface, and some of them have centers suggestive of central delling.

A violaceous border often is encountered in large plaques in morphea but infrequently is present in morphoea guttata. Gans clearly ascribed this violaceous color to a peripheral infiltrate about the papule in the midcutis (fig. 8*a*). An erythematous areola described as present in some cases of lichen sclerosus et atrophicus, especially in lesions in the early stages of the disease, can be explained pathologically on a similar basis. It is our contention that critical pathologic observation almost always will permit classification of doubtful examples of the condition either as morphea, which is simply a form of localized scleroderma, or as lichen sclerosus et atrophicus. Of course, it is possible that both diseases could occur at the same time in the same patient, just as one of us observed lesions of lupus erythematosus and of psoriasis occurring simultaneously in the same patient and even in the same lesion pathologically.[38]

37. O'Leary, P. A.: Personal communication to the authors.

38. Goeckerman, W. H.: Psoriasis Associated with Lupus Erythematosus, M. Clin. North America **15**:1491-1496 (May) 1932.

Acrodermatitis Chronica Atrophicans (Including Macular or Idiopathic Atrophy and So-Called Anetoderma).—There is a border zone between the atrophic epidermis and the infiltrate in the cutis, but there is definite atrophy of the entire cutis which does not occur in lichen sclerosus et atrophicus, and the other histologic features of lichen sclerosus et atrophicus are absent. The clinical picture is entirely a different one.

Lichen Planus.—The histologic picture of lichen planus is diagnostic and consists of increase in the stratum corneum and stratum granulosum

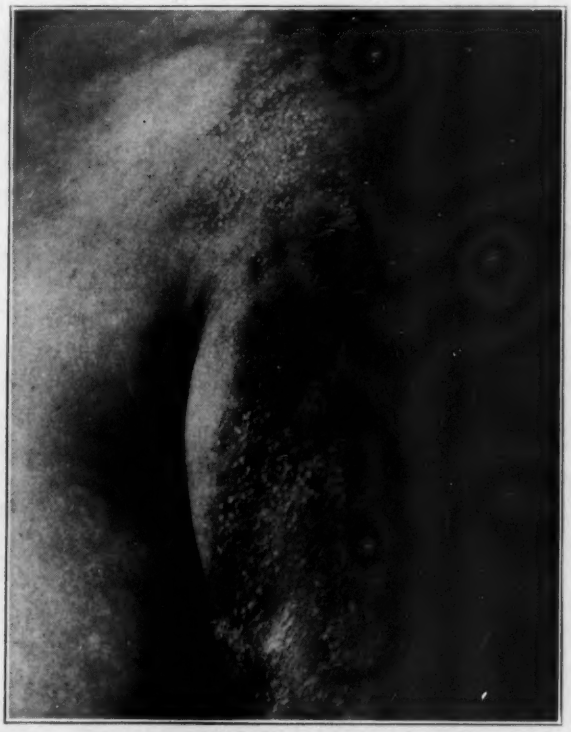

Fig. 9.—Morphoea guttata (localized scleroderma) simulating the clinical picture of lichen sclerosus et atrophicus. The histologic aspects are typically those of morphea.

with varying degree of acanthosis, pronounced liquefaction degeneration and necrosis of the basal cell layer and the presence of a dense infiltrate which is usually sharply limited to the upper portions of the cutis and which participates in the liquefaction necrosis of the basal cell layer. Even in atrophic forms of lichen planus, this infiltrate persists and even when the epidermis becomes decidedly thinned (fig. 8*b*). In none of the 19 instances of lichen sclerosus et atrophicus which we studied histo-

logically were the characteristic histologic changes of lichen planus revealed. In 1 case there was a dense infiltrate in the upper part of the cutis, which was separated, however, from the epidermis by a definite zone of edema similar to the condition in the case described by Grzybowski. We believe that the condition in his case was similar to the plaque type of lichen sclerosus et atrophicus. We made multiple sections in all our 19 cases of lichen sclerosus et atrophicus, and serial sections in 1 case, without encountering the histologic features of lichen planus. A varying degree of liquefaction necrosis of the basal cell layer may be seen in the presence of many other dermatoses. The regions of edematous homogenized connective tissue between the epidermis and the infiltrate deep in the cutis are distinctive of lichen sclerosus et atrophicus and are not seen in lichen planus. Clinically, in atrophic forms of lichen planus, whether the lesions are few or generalized, there is a tendency for increased pigmentation of the borders of the lesion to occur, and usually careful search will reveal one or more typical lesions of lichen planus with violaceous, polygonal, flat-topped papules. In lichen sclerosus et atrophicus, even from the beginning, the lesions are whitish. It is of considerable significance that in none of the 46 cases of lichen sclerosus et atrophicus that we studied at the clinic were there any lesions on the mucous membranes of the mouth, although Hallopeau reported such lesions as occurring in 1 of his cases. In lichen planus, involvement of the mucous membranes of the mouth is of frequent occurrence. Itching is not so prominent, so intense or so frequent a symptom in lichen sclerosus et atrophicus as it is in lichen planus. There is also relatively slower development of new lesions of lichen sclerosus and a greater tendency for chronicity of the disease as compared with ordinary lichen ruber planus. We have already referred to the erroneous classification in the literature of atrophic forms of lichen ruber planus as lichen sclerosus et atrophicus. It seems to us, therefore, that clinically, and most certainly pathologically, lichen sclerosus can be distinguished from atrophic forms of lichen planus.

Lupus Erythematosus.—The histologic picture is somewhat suggestive of disseminate forms of lupus erythematosus because of the keratotic plugs and lymphedema in the upper portions of the cutis, but edema and homogenization of the connective tissue are more evident than in lupus erythematosus.[39] There is no destruction of elastic tissue, such as occurs in lupus erythematosus, and clinically there are no constitutional symptoms, as are usually present in disseminate forms of lupus erythematosus, nor is the clinical picture at all similar.

Pityriasis Rubra Pilaris.—In pityriasis rubra pilaris and in vitamin A deficiency there is parakeratosis as well as hyperkeratosis in relation to

39. Montgomery, H.: Pathology of Lupus Erythematosus, J. Invest. Dermat. **2**:343-359 (Dec.) 1939.

keratotic plugs. Parakeratosis is not present in lichen sclerosus et atrophicus. There is a tendency in the recent literature to regard various types of follicular hyperkeratosis as being related to hypovitaminosis, especially vitamin A deficiency, but there was no history or suggestion of any real vitamin deficiency in any of the patients in our series.

Kraurosis Vulvae.—It is necessary to discuss kraurosis vulvae because it is the one condition in which the pathologic changes closely simulate and may even be indistinguishable from the histologic picture of lichen sclerosus et atrophicus and, secondly, because the two conditions have been confused with one another clinically, although the clinical pictures are entirely different. Kraurosis vulvae has been defined concisely by Darier [40] as follows:

> The term kraurosis (Breisky), the meaning of which is sufficiently vague, has been defined, due chiefly to the work of Jayle, and should be reserved for a sclerosing progressive atrophy of the mucocutaneous teguments of the vulva, leading gradually to stenosis of the vaginal orifice, the disappearance of the labia minora, the frenulum and the clitoris and flattening of the labia majora. The mucosa of the parts involved is always smooth, shining and dry. The color is white, waxy yellow, red, or spotted. Complication by leukoplakia is frequent. In such a case cancer is to be feared.

It should also be distinguished from simple senile atrophy of the vulva occurring postmenopausally.[41] In kraurosis vulvae the atrophic skin gradually merges with the normal skin, and kraurosis does not as a rule extend beyond the inner aspects of the labia majora.

The clinical picture of features of lichen sclerosus of the vulva is well shown in figure 4. Whitish papules with typical dells or plugs are present and merge to form a sharply defined plaque extending out onto the inner aspect of the thighs and also about the anus. Most of our patients who had vulvar lesions showed perianal involvement, which does not occur in kraurosis. Furthermore, the picture in figure 4, which is of a woman 65 years of age, shows no more atrophy of the vulvar parts than would be expected for a person of her age. There was no atresia or stenosis of the vaginal orifice to be seen, such as is characteristic of kraurosis vulvae.

In regard to the question of the relation of lichen sclerosus of the vulva to the menopause, the condition in our cases developed anywhere from eight months to twenty years after the menopause, and in 1 case lesions of lichen sclerosus were seen on the vulva in a child 10 years

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40. Darier, J.: Précis de dermatologie, ed. 4, Paris, Masson & Cie, 1928, pp. 276, 465 and 994.

41. Adair, F. L.; Davis, M. E., and Schuitema, D. M.: Atrophy of the Vulva, J. A. M. A. **114**:296-302 (Jan. 27) 1940.

old before any evidence of menstruation was present. In several instances lesions of lichen sclerosus were present for many years before the menopause.

The histologic changes which occur in lichen sclerosus and kraurosis are similar. In kraurosis there are relative and absolute hyperkeratosis, atrophy of the rest of the epidermis, some liquefaction necrosis of the basal layer and the same type of peculiar homogenization and separation of elastic tissue fibers from the epidermis as is seen in lichen sclerosus (resulting from lymphedema in the upper portion of the cutis and dilatation of lymphatic spaces, vessels and capillaries). In addition, in true kraurosis there are definite atrophy of the cutis as a whole and mild arteriosclerotic changes in the deeper vessels. Keratotic plugging as seen in lichen sclerosus usually is not present in kraurosis.

Why these dissimilar conditions should have a similar histologic picture is difficult to explain, but comparable instances are seen in regard to similar pathologic pictures of early stages of senile keratosis, lupus erythematosus or even hypertrophic lichen planus. In several instances in our series lichen sclerosus in which vulva and anus were involved occurred in elderly persons and were associated with intense pruritus. In case 1 (fig. *7 a*) there was some increased thickening of the epidermis suggestive of early leukoplakic changes. One of us (H. M.) [42] has previously emphasized the frequent association of kraurosis and leukoplakic vulvitis. The intense itching might in part be attributed to beginning kraurosis or leukoplakia and not necessarily to the lichen sclerosis et atrophicus. Finally, leukoplakia (leukoplakic vulvitis) is distinctive clinically and pathologically from lichen sclerosus et atrophicus.

SUMMARY AND CONCLUSIONS

Lichen sclerosus et atrophicus, we believe, presents typical clinical and histologic changes which are distinct from morphoea guttata on the one hand and from atrophic lichen planus on the other hand. Transitional forms between lichen sclerosus et atrophicus and morphoea guttata or atrophic lichen planus were not encountered in this series of 46 cases of lichen sclerosus et atrophicus. Most of such cases reported in the literature probably represent instances of one disease or the other. The terms "white spot disease" and "cardlike scleroderma of Unna" have been used loosely to include both lichen sclerosus and morphea, and it is suggested that these terms be abandoned. The histologic changes in lichen sclerosus are those of edema and homogenization of the connective tissue and keratotic changes in the epidermis. The pathologic

42. Montgomery, H.; Counseller, V. S., and Craig, W. McK.: Kraurosis, Leukoplakia and Pruritus Vulvae: Correlation of Clinical and Pathologic Observations with Further Studies Regarding Resection of the Sensory Nerves of the Perineum, Arch. Dermat. & Syph. **30**:80-100 (July) 1934.

changes are scarcely to be considered as those of true sclerosis of the connective tissue. The histologic changes are similar to those seen in kraurosis vulvae, from which condition lichen sclerosus et atrophicus can readily be distinguished clinically. Lichen sclerosus et atrophicus occurs about six times as frequently among women as among men, and in women it often begins on the vulva, without, however, there being any apparent relation of the condition to menstrual disturbance or to the menopause. The cause of lichen sclerosus et atrophicus remains to be determined.

ABSTRACT OF DISCUSSION

Dr. Oliver S. Ormsby, Chicago: In Dr. Montgomery's report of his extensive study of lichen sclerosus et atrophicus and allied conditions, he stated that this group was investigated and reported on by his father, the late Frank Hugh Montgomery, and me. At the time of our original report much confusion existed concerning the proper classification of a group of cases of white lesions, which up to that time had occurred chiefly in women and were largely limited to the upper portion of the trunk.

The first case of this group was described in 1901 by Westberg (*Monatsh. f. prakt. Dermat.* **33**:355, 1901) under the title "White Spot Disease." In 1903 J. C. Johnston and S. Scherwell (*J. Cutan. Dis.* **21**:302, 1903) described a second case. In 1907 the late Dr. Frank Hugh Montgomery and I (ibid. **25**:1, 1907) described 2 cases we had had under observation for some years, together with a typical case of lichen planus sclerosus et atrophicus, and discussed 8 previously recorded cases. Our conclusions were that all these cases were instances of lichen planus sclerosus et atrophicus or morphoea guttata. In 1910 (Ormsby, O. S.: Lichen Planus Sclerosus et Atrophicus [Hollopeau], *J. A. M. A.* **55**:901 [Sept. 10] 1910), I reported on the clinical and histologic study of 6 cases and reviewed the literature to that date, with the same conclusions. In 1938 at the St. Louis meeting of the Academy of Dermatology and Syphilology, in the discussion of a case of Csillag's disease (dermatitis lichenoides chronica atrophicans), I again reviewed the whole subject (Arch. Dermat. & Syph. **40**:132 [Aug.] 1939).

Dr. Montgomery considers lichen sclerosus et atrophicus an entity and not related to lichen planus. He also discussed with propriety kraurosis vulvae, which in some cases resembles members of the group under discussion.

(Dr. Ormsby demonstrated the clinical picture with slides showing: white lesions on the upper portion of the chest and back [first cases of Montgomery and Ormsby], morphoea guttata on the chest with scleroderma on the leg of the same patient, morphoea guttata on the shoulder and typical lichen sclerosus et atrophicus with lesions on the shoulder, both front and back. All of these conditions occurred in women.)

In conclusion, it is interesting to note that in his extensive and careful study Dr. Montgomery confirms the observations made many years ago by his father and me and adds kraurosis vulvae for differentiation.

Dr. Ruben Nomland, Iowa City: My opinions are based on a study of 7 cases of lichen sclerosus et atrophicus and 2 of cardlike scleroderma. I am inclined to agree with Dr. Montgomery that lichen sclerosus et atrophicus is clinically and pathologically an entity that is different from any other disease and, at least in my opinion, not related to lichen planus.

I wish to differ slightly with Dr. Montgomery in his interpretation of his pathologic findings. I believe—and I think his slides showed it well—that primarily there is edema and homogenization of the superficial portion of the cutis and that the latter goes on to sclerosis, although, as he defined sclerosis, one would hesitate to say there is sclerosis.

To say, from his slides, that elastic tissue was present in an almost normal fashion requires a stretch of the imagination. As far as I could tell, the elastic tissues were a great distance below the atrophic epidermis. So I should say that pathologically there is at first edema, then homogenization and later, simultaneously to some extent, sclerosis, with atrophy and disappearance of the elastic tissue.

Dr. Henry D. Niles, New York: I have encountered several of these cases, and I have had the same experience as Dr. Montgomery, that the majority of the patients have been women. I think that that finding may be significant. I wonder if he has considered the possibility of an endocrine background.

Most of my patients have been middle-aged women, at or beyond the menopause. Treatment is one feature of this disease that has not been discussed yet and which is rarely mentioned. It is rather embarrassing after a while when a physician has a patient with this condition. It is a rare and interesting condition, and he wants to show the woman to his students, but she cannot keep coming to the clinic forever if she does not get help.

The only thing I have been able to do is to give these patients a 2 per cent ointment of salicylic acid which causes the plugs to peel off. The patients look better temporarily, so they keep coming for a while for demonstration. I wonder whether possibly some estrogenic hormone might be of value. In some of these cases the condition is associated with kraurosis vulvae, and that condition is sometimes improved by endocrine therapy.

Another point is the localization, which Dr. Ormsby mentioned. Almost all of my patients have had lesions on the upper parts of the chest, back and shoulders. In fact, I have not seen any patients who had lesions elsewhere. There must be some reason for this localization that is not known.

Dr. Fred D. Weidman, Philadelphia: The only phase of the presentation which I care to discuss is the interpretation of the features which are shown in the histologic sections. My mind ran much the same as did that of Dr. Nomland, namely, believing that the fundamental, essential process was a hydropic one; Dr. Nomland called it edema. Perhaps I would prefer the term "imbibition"—a hydropic imbibition on the part of the fibrous tissue whereby the original kind of connective tissue came to contain a larger proportion of water than it originally did.

As I interpret these changes in Dr. Montgomery's sections, and as I have seen them in my own, this tissue should have a much softer, more jelly-like consistency than what would be expected from the appearance of the tissues clinically, that is, from their dead white and scarlike appearance. Some weight is given to that impression from the fact that a space appears rather consistently between the basement membrane of the epidermis and the mass of fibrous tissue below—something commonly called an artefact. But it is not artefact alone. It really gives some information. It indicates that under the influence of the fixative the pathologic tissue below is being influenced in a different way from the tissues of the epidermis and the tissue of the corium at large; that is, it is being contracted more decidedly than the other tissues. The same considerations apply in sections of basal cell cancer. Cancer cells are commonly contracted upward toward the surface, with a space (a hiatus) between the palisade layer of the

basal cells and the fibrous tissue of the corium underneath. This indicates that the substance of that particular example of basal cell cancer was more watery, softer and more gelatinous. I think, too, that in colloid degeneration of the skin one gets much the same effect. There, again, is a homogeneous, clear kind of tissue, just as Dr. Montgomery has shown in lichen sclerosus et atrophicus. All dermatologists are familiar with the broad clefts that traverse these masses. These considerations, involving as they do a more or less homogeneous substance (at least in the case of the colloid and these cases of lichen sclerosus et atrophicus), point to the presence of a larger amount of water within their fibrous tissue.

In studies many years ago on the nature of edema in nephritis, Fischer experimented with blocks of gelatin and found that by altering their p_H he could influence the amount of water which they would take up. When this measured block of gelatin was impregnated with extremely dilute acid, for example, and subjected to the same environmental conditions as to moisture, the block which had the lower p_H (the more acid) would swell up to a greater extent. I surmise that lichen sclerosus et atrophicus fundamentally is not inflammatory but that it is referable to some physicochemical change in the fibrous tissue. That is as far as one can go today in the way of interpretation of the changes in tissue seen in histologic sections. After that, it is a matter of whatsoever studies in microchemistry that might be devised, if they are available at all. But in any event, I think that that is the starting point for an inquiry into the fundamental pathology of this condition. That is, what factor is it that leads to an increased imbibition of water by this collagenous tissue?

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I agree with Dr. Weidman that the pathologic changes in lichen sclerosus et atrophicus are entirely different from an inflammatory type of reaction seen in lichen planus or the fibrotic and sclerosing changes seen in scleroderma, including morphoea guttata. The edematous changes seen in the upper cutis in lichen sclerosus suggested the possibility of mucinous or colloid-like changes, but special stains failed to reveal these substances. There were no general symptoms of any significance and no special systemic diseases associated with lichen sclerosus. In none of the cases of lichen sclerosus et atrophicus were there any lesions clinically suggestive of lichen planus papules. Subjective symptoms of lichen sclerosus are usually minimal.

Whereas there is a predilection for the lesions to occur on the shoulders and trunk, they may be seen anywhere. The lymphedema in the upper part of the cutis is not an artefact but in many cases results from true dilatation of lymph vessels.

I can understand why Dr. Nomland wants to say there is destruction of elastic tissues, and perhaps to a slight extent this is true. Careful studies, however, reveal that the decided degree of lymphedema and the homogenization of the connective tissue fibers result in separation of the epidermis from elastic fibers in the cutis which still retain their pattern as they originally were arranged in the papillary bodies. This phenomenon also occurs in kraurosis vulvae. Changes in the elastic tissue are entirely different from those seen in scleroderma, and in the latter condition there are also obliterative changes in the blood vessels.

No satisfactory method of treatment is known. There may be periods of remission and exacerbation. Of 18 cases which we were able to follow, new lesions developed in a few and in some instances the lesions had undergone involution.

THE PERSONALITY FACTOR IN PSYCHONEUROGENOUS REACTIONS OF THE SKIN

JOHN H. STOKES, M.D.
PHILADELPHIA

To understand and use the progress made in knowledge of psychoneurogenous mechanisms for purposes of etiologic analysis and treatment, it should be insistently reiterated that cause and remedial procedure in disease are to be thought of as complex and multiple rather than as simple and sole. The psychoneurogenous factor, like the focal infective, the bacterial, the toxic and the traumatic factor, rarely seems to act alone. It is part of an interplay—an affair of predispositions and excitants, of broadening and narrowing influence, as one or another element approaches, recedes from, collides with or combines with other factors in the causal complex. Among the newest of the new factors elbowing their way into place in the thinking of the analyst of disease causation is the psychosomatic concept of the "total personality." This paper is an attempt to place the personality of the person with neurodermatitis in some definitive relation to the behavior of his skin, again, not as a sole cause of his trouble but as a factor acting in a complex of hereditary, physiologic, allergic, bacteriologic, immunologic and other pathogenic and protective-reactive agencies.

A decade has seen a remarkable transformation from the day when a polemic could be written on neurogenous versus contact irritant background [1] to that of the impressive catalogue of the neurodermatoses, hardly completed, recently published by the psychiatrist Gillespie [2] in a dermatologic journal. The analysis by Klaber and Wittkower [3] of the emotional background of the person with allegedly demodex-caused rosacea complex,[4] Pearson's [5] study of psychogenous conditioning in 3

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Read before the Section on Dermatology at the Ninety-First Annual Session of the American Medical Association, New York, June 12, 1940.

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2. Gillespie, R. D.: Psychological Aspects of Skin Diseases, Brit. J. Dermat. **50**:1, 1938.

3. Klaber, R., and Wittkower, E.: The Pathogenesis of Rosacea: A Review with Specific Reference to Emotional Factors, Brit. J. Dermat. **51**:501, 1939.

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cases of inflammatory cutaneous eruptions and the observations of Grant, Pearson and Comeau [6] and of Hopkins, Kesten and Hazel [7] on the conversion of anger into cholinergic urticaria are other examples in point. Psychosomatic integrations so profoundly concern all dermatologists and allergists, to say nothing of many other "ists" and "icians," including general practitioners, that they are here summarized.

The cholinergic, or histamine body, mechanisms now include the groups foreshadowed by Lewis [8] and demonstrated by Grant, Pearson and Comeau [6] of the emotionally induced urticarias and urticarial dermatitides dependent on the liberation of "H substances," probably acetylcholine, at nerve terminations under psychic stimuli, such as anger.

The gastrointestinal mechanisms through which emotion influences the skin include a wide range of depressant and accentuating effects on secretion,[9] tone and motility,[10] absorption of minerals,[11] production and

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7. Hopkins, J. G.; Kesten, B. M., and Hazel, O. G.: Urticaria Provoked by Heat or by Psychic Stimuli, Arch. Dermat. & Syph. **38**:679 (Nov.) 1938.

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absorption of allergens,[12] favoring of local and widespread infective processes,[13] chronic changes in bacterial flora and their chemical products suggesting linkage with histamine body mechanisms [14] by absorption and vitamin absorption and utilization [15] under emotionally induced gastrointestinal secretory states. It is interesting to note the emphasis Klaber and Wittkower [8] placed on gastric tone as distinguished from secretory chemistry in the argument over rosacea and to speculate on the extent to which facial flush, low blood pressure and a depressive emotional state resemble the behavior, in extended form, of a person who has received a dose of histamine hypodermically.

The third group of psychoneurogenous mechanisms includes those concerned with the emotionally controlled apocrine sweat glands,[16] which probably influence, for example, the distribution and behavior of the now rather common "streptolevurids" or intertriginous eczematoid manifestations in the groin, perigenital, perianal, submammary, axillary and periumbilical areas—the infection-allergic complex described by Darier [17] ("parakeratosis psoriasiforme"), Ravaut and his associates [18]

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13. Nye, R. N.; Zerfas, L. G., and Cornwell, M. A.: The Presence and Importance of Yeast-Like Fungi in the Intestinal Tract, Am. J. M. Sc. **175**:153, 1928. Ricen, L.; Sears, H. J., and Downing, L. M.: The Duodenal Flora in Achlorhydria, ibid. **175**:386, 1928.

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16. Way, S. C., and Memmesheimer, A.: The Sudoriparous Glands: II. The Apocrine Glands, Arch. Dermat. & Syph. **38**:373 (Sept.) 1938.

17. Darier, J.: Précis de dermatologique, ed. 4, Paris, Masson & Cie, 1928.

18. (*a*) Ravaut, P., and Rabeau, H.: Parakératoses psoriasiformes, sèches et lévurides, Presse méd. **36**:1443, 1928; (*b*) Réactions cutanées à type de parakératose et d'eczéma, provoquées par l'injection intradermique de levurine chez un malade atteint depuis quatorze mois d'intertrigo et d'eczéma, Bull. Soc. franç. de dermat. et syph. **36**:170, 1928. (*c*) Ravaut, P.: Les eczématides secondaires d'origine allergique survenant au cours des intertrigos à levures (Lévurides), Bull. Acad. de med., Paris **101**:680, 1929. (*d*) Ravaut, P.; Rabeau,

and Ramel [19] from various angles. It seems probable that more intensive study will also tend to enlarge the importance of the nerve-influenced sweat mechanism of eccrine origin in some of its regional (palmar, cubital and popliteal) anomalies of activity.

The vasomotor congestive reactions are a fourth field of current psychoneurogenous correlation. Stigmatization under hypnosis and in hysteroid states [20] seems now an established phenomenon; but far more important are the tie-ups between the flush, or blush, and the feelings of inferiority and guilt, which are now used by dermatoneuropsychiatrically inclined observers in their causal theories. The recent publications of Mittelmann and Wolff [21] and of Ziegler and Cash [22] on temperature of the skin (i. e., vasomotor and perhaps sweat) emotional correlations have important bearings on the circulatory response in the skin to emotion. It is even possible for the humble practitioner and the clinician to observe both stigmatization in the congestion of dermatitic lesions on the extremities and color play in dermatitis of the face and neck under the come and go of emotional stress and mental catharsis at bedside and office. Occasionally it is possible to bring about by psychotherapy lasting, almost Lourde-like miracles of confessional facial ischemia, as one might call it.

A fifth group of integrations concerns the phenomena of suggestion-induced and suggestion-modified allergic responses, with and without hypnosis. Considering the rather general acceptance of the psychogenous factor in asthma, it is curious to see similarly applied considerations in the pruriginous and neurodermatitic phases of reactivity of shock tissue so hotly resisted by some dermatologists and allergists. A steadily accumulating body of evidence indicates that the threshold of allergic reactivity of shock tissue can be increased or decreased by the more direct access to the lower emotional centers afforded by hypnosis. What is more important for practical dermatology, well authenticated examples

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H.; Longhin, and Koang: Intertrigos à localisations multiples. Eczématides secondaires des bras et des jambes. Présence de levures et de streptocoques dans les intertrigos. Réactions biologiques, Bull. Soc. franç. de dermat. et syph. **37**: 561, 1930.

19. Ramel, E.: Du rôle des levures dans la pathogénèse des dermatoses, Rev. méd. de la Suisse Rom. **49**:887, 1929.

20. Klauder, J. V.: (*a*) Psychogenic Aspects of Skin Diseases, J. Nerv. & Ment. Dis. **84**:249, 1936; (*b*) Stigmatization, Arch. Dermat. & Syph. **37**:650 (April) 1938.

21. Mittelmann, B., and Wolff, H. G.: Affective States and Skin Temperature: Experimental Study of Subjects with "Cold Hands" and Raynaud's Syndrome, Psychosom. Med. **1**:271, 1939.

22. Ziegler, L. H., and Cash, P. T.: A Study of the Influence of Emotions and Effects on the Surface Temperature of the Human Body, Am. J. Psychiat. **96**: 677, 1938.

of the appearance and disappearance of allergic reactivity of the skin [23] under varying states of mind are beginning to accumulate. They have long been recognized in asthma.[24]

One of the extremely important interrelations involved in emotion-allergic phenomena concerns allergy of infection. What is it that makes infectious asthma flare [25] when the patient receives a disturbing letter? Is there not reason to believe that emotion can broaden the allergic base [26] in much the same way as does a sensitizing sinus or other infection?

Correlations between streptomycotic intertriginous eruptions and emotional, particularly sexual, stresses and between pyogenic-contact allergic eruptions of the hands and shock or tension often impress both observer and patient. Shifts in the allergic pattern of patients with neurodermatitis take place even with active allergens.[27]

I do no more than mention here what should be the sixth and seventh groups of emotionally influenced mechanisms of cutaneous reaction, the endocrine factors and the dextrose metabolism factors,[28] because while there is every reason to believe that something tangible will emerge from both directions, as yet one sees only the draped outline of an elbow or a knee thrust out from behind an as yet discouragingly opaque curtain of conflicting statement and imperfectly controlled procedure. Just how emotion, which undoubtedly influences endocrine function and dextrose metabolism, affects the skin through them is as yet largely unknown and not too well guessed.

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23. Pattie, F. A.: The Genuineness of Hypnotically Produced Anesthesia of the Skin, Am. J. Psychol. **49**:435, 1936. Marcus, H., and Sahlgren, E.: Untersuchungen über die Einwirkung der hypnotischen Suggestion auf die Funktionen des vegetativen Systemes: IV, Acta psychiat. et neurol. **11**:119, 1936. Diehl, F., and Heinichen, W.: Psychische Beeinflussing allergischen Reaktionen, München. med. Wchnschr. **78**:1008, 1931.

24. Moos, E.: Kausale Psychotherapie beim Asthma bronchiale, München. med. Wchnschr. **70**:805, 1923. Dunbar, H. F.: Psychoanalytic Notes Relative to Syndromes of Asthma and Hay Fever, Psychoanalyt. Rev. **7**:25, 1938. McDermott, N. T., and Cobb, S.: A Psychiatric Survey of Fifty Cases of Bronchial Asthma, Psychosom. Med. **1**:203, 1939.

25. Harkavy, J., and Maisel, F.: Infectious Asthma and Its Relationship to Chronic Sinus and Pulmonary Disease, J. A. M. A. **96**:1843 (May 30) 1931. Harkavy, J., and Hebald, S.: Association of Infectious Asthma and Arthritis from Point of View of Bacterial Allergy, Arch. Int. Med. **49**:698 (April) 1932.

26. Bloch, B.: Pathogenese des Ekzema, Arch. f. Dermat. u. Syph. **145**:34, 1924.

27. (*a*) Hansen, K.: Analyse, Indikation und Grenze der Psychotherapie beim Bronchialasthma, Deutsche med. Wchnschr. **53**:1463, 1927. (*b*) Rogerson, C. H.: The Psychological Factors in Asthma-Prurigo, Quart. J. Med. **6**:367, 1937.

28. Dunbar, H. F.: Emotions and Bodily Changes, ed. 2, New York, Columbia University Press, 1938.

Next to be considered are the eighth and ninth fields of psychosomatic correlation, the eczema–prurigo or eczema–asthma–hay fever personality and what I here designate as the tension frame of mind. Thanks to the work of Drake,[29] Rogerson and his associates [30] and Strauss [31] in Gillespie's clinic at Guy's Hospital, the gropings of previous less trained analysts and observers have been crystallized into a clearcut picture of what makes the asthma-prurigo (Besnier) personality distinctive; and the distinctive features have been proved to have etiologic import by therapeutic test.[27b] Less clearcut as yet are the outlines of the other types of neurodermatitic reactant personality—the subjects of emotional urticaria, acute exudative neurodermatitis, the rosacea complex and the catalogued dermatoses of Gillespie's summary. In fact, in attempting to describe the latter phase, I venture to act only as an interested amateur, whose gropings may precede an illuminating delineation at the hands of a trained psychiatrist that will bring this type to a par with the present comprehension of the eczema–asthma–hay fever personality.

How may one suppose that the nine groups of psychosomatic correlations act in a given person? Are there clinical pictures distinctive of a preponderance or sole presence of one or another element? The cholinergic urticaria often seems an entity in itself, yet critical examination of cases of chronic urticarias [32] discloses that the conditions are reactions of multiple causation for which relatively seldom does an emotional cause appear alone. Emotion, like allergy, probably has its shock structures, lending some constancy to picture or trend, as in what I once called familial "cutaneous tears"; but heredity, focal infections, drugs, and metabolic quirks usually load the gun if they do not pull the trigger. The interplay between emotion and infection, emotion and allergy, emotion and sweat and emotion and vasomotor mechanisms furnishes some of the most complicated of present problems, of increasing importance in my field of observation at least.

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29. Drake, J. A.: The Asthma-Eczema-Prurigo Complex, Brit. J. Dermat. **40**:407, 1928.

30. (*a*) Rogerson, C. H.; Hardcastle, D. H., and Duguid, K.: A Psychological Approach to the Problem of Asthma and the Asthma-Eczema-Prurigo Syndrome, Guy's Hosp. Rep. **85**:289, 1935. (*b*) Rogerson, C. H.: The Role of Psychotherapy in the Treatment of the Asthma-Eczema-Prurigo Complex in Children, Brit. J. Dermat. **46**:368, 1934.

31. Strauss, E. B.: The Psychogenic Factor in Asthma: I. A Problem in Methodology, Guy's Hosp. Rep. **85**:309, 1935.

32. Stokes, J. H.; Kulchar, G. V., and Pillsbury, D. M.: Effect on the Skin of Emotional and Nervous States, Arch. Dermat. & Syph. **31**:470 (April) 1935. Urbach, E.: Kritische Uebersicht über 500 eigene Urtikariafälle, München. med. Wchnschr. **84**:2054, 1937. Hopkins, J. G., and Kesten, B. M.: Urticaria: Etiologic Observations, Arch. Dermat. & Syph. **29**:358 (March) 1934.

ECZEMA–ASTHMA–HAY FEVER OR ASTHMA–PRURIGO PERSONALITY

The typical eczema–asthma–hay fever temperament develops in persons who are the second, third and even fourth generation descendants of nervously intense and high-strung allergic persons (Stokes [33] and Rogerson [27b]). As so often occurs in emotion-allergic complexes, it is difficult to decide which is cart and which is horse in the pair. But so true is it in my experience that a family history of tension and instability coupled with allergy is a primary essential to the diagnosis of the eczema–asthma–hay fever complex that I give a distinctly different prognostic and therapeutic rating to the more nearly pure allergic subject of a single generation's standing, so to speak. With the latter, it is often sufficient to exclude the allergens, usually few and clearcut. It is necessary to remake the person with the true eczema–asthma–hay fever complex, with far more emphasis on the psychogenous background. Several generations of the emotion-allergy combination produce the "diathetic" or eczema–asthma–hay fever person. Moreover, the distinctive combination does not affect all siblings but shows a distinct disposition to appear in scattered instances in a family,[34] though this scattering is probably influenced by other inheritable anomalies,[35] such as susceptibility to pyogenic infection and ichthyosis, as well as by the first, second and third child position in the family, familiar to psychiatrists as a personality-molding influence. While the order or sequence of characteristics and their interrelations is matter for argument, the best work on the subject plus my personal impressions provide the following list:

1. A deep-seated feeling of insecurity.
2. An easily developed feeling of inferiority.
3. Aggressiveness, disposition to dominate and to command attention, a species of drive possibly compensatory for qualities 1 and 2 but also including an element of quality 4.
4. An intense self consciousness or I-sensitiveness, the "liebe ich" ("beloved I") of the German literature; this is less a vulgar and robust egotism than it is a kind of ultrasensitiveness, like hypersensitiveness to physical pain.

33. Stokes, J. H.: (*a*) Diathetic Eczema: The Cutaneous Phase of the Eczema-Asthma-Hay Fever Complex, M. Clin. North America **15**:279, 1931; (*b*) The Eczema Problem, Am. J. M. Sc. **179**:69, 1930; (*c*) The Complex of Eczema: A Diagnostic and Etiologic Analysis, J. A. M. A. **98**:1127 (April 2) 1932; (*d*) The Nervous and Mental Component in Cutaneous Disease, Pennsylvania M. J. **35**:229, 1932; (*e*) Functional Neuroses as Complications of Organic Disease: An "Office" Technic of Approach with Special Reference to the Neurodermatoses, J. A. M. A. **105**:1007 (Sept. 28) 1935.

34. Hanhart, E.: Erbklinik der Idiosynkrasien des Heufieber als Leitsymptom allergescher Veranlagung, Deutsche med. Wchnschr. **60**:1163, 1934.

35. Stokes, J. H., and Sternberg, T. H.: A Factor Analysis of the Acne Complex with Therapeutic Comment, Arch. Dermat. & Syph. **40**:345 (Sept.) 1939.

5. Marked lability of physical and mental reaction, which in some becomes adaptability and in others instability.

6. An intrinsic kinetic drive, a species of thalamic pressure (I tell patients they carry 500,000 kilowatt generators in their brain stems), which is probably interwoven with or causative of quality 3 and which is at the bottom of quality 7.

7. An all-or-none type of reactivity, a species of spark-over which knows no half-way or compromise approaches to problems or to reactions to stimuli (with spasmophilia as a physical expression?), plus qualities 8 and 9.

8. A higher than average intelligence quotient.

9. Tension, expressed or repressed.

10. Restlessness which is not instability but which is due to the rapid exploration and exhaustion of a subject, a problem or a possibility by a high pressure mind of exceptional capacity. The constant exhaustion of the possibilities of the moment or the situation leads to boredom and flight rather than to exhaustion and rest.

11. A deep-seated overdependence, the product of qualities 1 and 2, with traces of qualities 3 and 4.

12. A special reactiveness to competition, human and personal, possibly a product of qualities 1, 3 and 4.

It will be easily evident that a characterologic makeup such as this is certain of a tempestuous existence in which repercussions onto the gastrointestinal, secretory and motor mechanisms, the vascular and sweat systems, the endocrine and metabolic machinery and the allergic state are to be expected. While such a makeup may provide a basis for complexes in the technical sense, it is replete with basis for conflict and especially, as Rogerson [27b] has pointed out, for conflict between the disposition to dominate, with aggressiveness, and that of overdependence and oversolicitude, based on deep-seated insecurity. It is not a complex but a conflict, according to Rogerson, that underlies the diathetic person's trouble with his skin and bronchial reactions.

The interrelations between the elements listed provide the rationale of a readjustment program for asthmatic children (and their parents), which under Rogerson and Strauss [36] has cleared the Southampton asthma retreat of Guy's Hospital of patients, who now largely carry on in complete freedom or at a greatly improved status at home. That something similar can be accomplished for the prurigo-eczema subject must await (*a*) the sufficiently skilful application of the methods of Rogerson and Strauss to eczema–asthma–hay fever children before puberty and to their parents and (*b*) the development of less tedious, more direct, yet safe and effective methods of getting at the adolescent or adult personality, such as suggestion under threshold anesthesia, superficial

36. (*a*) Rogerson, C. H.: Personal communication to the author. (*b*) Strauss, E. B.: Personal communication to the author.

hypnosis and simpler reeducational processes short of deep psychoanalysis, which, in occasional cases I have observed, has done more harm than good.

Notwithstanding this somewhat pessimistic estimate of the immediate outlook for the undoubtedly promising psychotherapy of the eczema–asthma–hay fever patient, it is possible for the not too busy dermatologist or dermatoneuropsychiatrist to do something worth while for a person with this diathesis. It is remarkable how early in life insecurity, aggressiveness, I-consciousness or I-sensitiveness, drive or hyperkineticism and the conflict-inducing overdependence can be recognized. Insecurity seems almost part of prenatally determined mental structure in some children and aggressiveness in others. Both are usually fed by the adults in charge, especially when there is an unhappy marriage, an unwanted child or an overwanted child (oversolicitude) who serves as an outlet for pent-up or frustrated affection. Strauss [36b] stated that the 6 month old infant knows whether its parents love each other. The displacement of the first child by the second or of a second by a third may precipitate the latent elements of the conflict between aggressive dominance and overdependence and transform a previously well child into an asthmatic, cutaneous, gastrointestinal or allergic cripple. The early recognition of the elements in the situation becomes almost instinctive with practice, and one can spot the hyperkineticism and the demand for attention, the restless curiosity thrown into reverse by flight to the mother's skirt or knee, in one's office waiting room before the child is examined. It is essential to single out the oversolicitous and the antagonistic adults (not always a parent, perhaps a nurse or relative) and then to proceed according to Rogerson's suggestion, with 60 per cent of the time devoted to ironing out the damaging adults and 40 per cent to reeducating the child. The egocentric reactivity of these children makes, as I have said, social pressure and example rather than parental or tutorial instruction their best teacher, and social pressure is exerted not by the physician, and least of all by the parent, but by equals in the playroom and the nursery and other schools. Immense effort must often be exerted to call off or hold back the adult disturbing factors in the case. One of the curious paradoxes of human behavior is the development of resentment in the dominated parent, often the one of the opposite sex from the patient and the one who should naturally be attracted; this situation, of course, only feeds the conflict.

The most serious thing that can happen to the diathetic child, I believe, is to be driven in on himself by discipline, repression and severity—by "don'ting" as distinguished from trial and error doing. This produces the poker face, as I call the facial cast of the veiled and inaccessible personality, that defies ordinarily available methods of approach in later childhood, adolescence and in the adult. Children of

eczema–asthma–hay fever stock must be raised like the children of Bali, with infinite patience and by persuasion rather than by injunction and force.

The problems of the adult eczema–asthma–hay fever personality may be framed roughly in this way. He will have trouble growing up, since his modes of reaction tend to be primitive and infantile, conditioned by insecurity and I-consciousness, with a need to enjoy a dependence that is flatly incompatible with his driving urge to dominate. His first problem in adjustment, then, is that of learning self acceptance; his second, that of impersonalization or depersonalization of life. As he solves these problems, he slowly and painfully acquires the basis of serenity and detachment, which are the signs, among others, of the truly adult mentality.[37] Next, in a world of fellow men, beset with everlasting noes, with stones of stumbling and rocks of nonacquiescence and inflexible offense, he must learn to discharge his thalamic energies without getting his front crumpled or his rear kicked off. The peculiar irritative reaction of his I-sensitiveness to the human competitor (he seems less antagonized by nature and by God!) and his inability to accept second place for himself in anything make competitive activity particularly hard on him. Often with a peculiar and poisonous joy, capable of winding him up to the breaking point, he pursues with ardor the very competitive activities and destinationism which are his undoing.

His next problem, and in many respects his most difficult one, is that of rest. Early in childhood these personalities begin to establish a rest deficit which mounts with the years. First goes the midday nap, then the early bedtime. Excessive study shortens the nights, and social strivings and "dates" presently abolish them altogether. Rogerson has well pointed out in one of his latest papers [27b] that the pseudo resting appearance of the eczema–asthma–hay fever child—even his very motionlessness—is tension and not rest after exhaustion. Nothing is outwardly more inexhaustible than the fund of energy of the person with the eczema–asthma–hay fever complex. Yet nothing by its constant outgo, without compensatory recuperative inactivity and relaxation, contributes more to the imbalance, the spasmophilia and the jittery instability of sweat and vascular mechanisms veiled behind the poker face. Therapeutically it is so easy for the physician to order rest and it is so difficult for the patient to secure it, without special training in relaxation. Moreover, it is not sufficient to prescribe rest by relaxation, for rest not only is dependent on a technic for release of tension but requires one for discharge of tension as well. In the eczema–asthma–hay fever patient's makeup, the slightest breath of competition and destination or of placement and achievement, as I have said, spells the end of capacity

37. Classically phrased by W. Lippmann (A Preface to Morals, New York, The Macmillan Company, 1929). Stokes.[33e]

to impersonalize, to view with serene detachment and, hence, to relax. So he must to varying degrees leave competition behind him and set out to explore the world of the moment, literally on foot—for walking is his cheapest and best resort.

The final problem of the person with the eczema–asthma–hay fever complex is to keep his hypersensitive ego and his dominance proclivities, great enemy makers that they are, from precipitating him in successive rebuffs back on his always waiting inferiority and insecurity; for if he is beaten back he will tend to conceal both his injured self esteem and his seething resentment at the defeat of his dominance behind the mask of the poker face. It must be apparent that in this succession of problems in personality there is ample material for a seriously disordered physical organization from the functional standpoint—that the cold sweat and the angry flush, the pale rage and the purple shame will play disastrously across a skin that packs such spiritual dynamite into the body it encloses. The wonder is not that so little can be done but that anything at all helpful can be done with a person like this.

THE TENSION FRAME OF MIND

This term was adopted, be it recalled, to identify the fundamental personality tone of the person with neurodermatitis whose condition does not conform to the complete picture of the eczema–asthma–hay fever complex. It is possible that the term really describes only the vagotonic type of neurodermatitis and that some other phrases should be coined to cover the mental state of the depressed, subdued and inwardly timorous victim of "social anxiety," which Klaber and Wittkower observed was more or less characteristic of subjects with rosacea. On the other hand, the same fundamental elements appear in the personalities of both outspoken and reserved types, though the reactions to them may be different or may even alternate in the life history of a given person. Tension personalities exhibit the basic sense of insecurity, rendered into fear of inadequacy, fear of failure and fear of not measuring up to a standard which is usually set at exaggerated performance levels by the same I-sensitiveness which appears in the eczema–asthma–hay fever personality. This combination of I-sensitiveness and fear of inadequacy is the mother of a conscientiousness whose child, in turn, in the life of the tension personality is the sense of the obligatory—the "must" and the procession or endless succession of "musts." "I must" in such persons is in eternal conflict with "I can't" or "I don't want to." The struggle too often winds up the personality to the creaking-cracking point and then, as in a clock without escapement control, lets the mainspring whirr loosely to temporary collapse.

But one must not allow an addiction to metaphor to gloss over the real difficulty of defining just what ails these persons and what should

be done to help them. If there is such a thing as a therapeutic test of the foregoing theorization, it appears in the striking improvements that follow the abandoning of the "musts," the temporary repudiation of conscience and the dropping of aim, objective, ideal and destination, with a lapse into purposeful purposelessness and masterly though undutiful inactivity.

It is hardly necessary here to go into the affect-effect mechanism of tension which is now almost a commonplace of psychodynamics [33]—the conversion of the thought of "must be doing," even without actually doing, into muscle tension, which most probably involves the acetylcholine or cholinergic mechanism of Dale [38] and others. It is even conceivable that the tense or wound-up person floods himself with acetylcholine beyond the capacity of his enzymatic release mechanism to neutralize and suffers, in some phases of his disability and reaction, from chronic low grade intoxication with an acetylcholine-like substance. In learning the first steps to relaxation of tension through the procedures of Call [39] and Jacobson,[40] the patient with a tension personality has a chance to see how differently he feels when he forgets his "musts." The core disappears from most anxieties when the patient is convinced that he can do nothing about the obligations involved and that his I-sensitiveness should not be affronted by his repudiation of responsibility.

Again, it should not be overlooked that the tension personality has much in common with the eczema–asthma–hay fever personality. The tension-exhaustion relations described by Rogerson [27b] and by myself [33a] for the latter can be reduplicated in the former. Hence the problem of differentiating in the patient between quietude due to exhaustion (which it seldom is) and quietude due to controlled tension is the same in both. In both, the problem of the poker face is the same and has led more than one dermatologist into disregarding a neurogenous background because a calm-faced patient with lichen planus or neurodermitis localizata stated that he had nothing to worry about. In both types the problem of rest deficit is much the same, for both are hounded over the road of life by I-sensitiveness that will not brook failure, repudiation of "ideals" or even second place and by a fear—the fear of inadequacy—

38. Dale, H. H.: (*a*) Croonian Lectures on Some Chemical Factors in the Control of Circulation, Lancet **1**:1179, 1233 and 1285, 1929; (*b*) Addresses Delivered at Dedication Exercises of Lilly Research Laboratories, Indianapolis, Ind., private publication of Eli Lilly & Co., 1934, p. 59.

39. Call, A. P.: Nerves and Common Sense, Boston, Little, Brown & Company, 1909; Power Through Repose, ibid., 1909.

40. Jacobson, E.: Progressive Relaxation: A Physiological and Clinical Investigation of Muscular States and Their Significance in Psychology and Medical Practice, Chicago, University of Chicago Press, 1929; You Must Relax: A Practical Method of Reducing the Strains of Modern Living, New York, McGraw-Hill Book Company, 1934.

grounded in inferiority and insecurity. The difference in the outlook and the comparative amenability of the tension personality to treatment seem to me to lie precisely in the domain of ingrained thalamic emotional reaction patterns which I have suggested as hereditary and congenital from my limited observation of infants with the eczema–asthma–hay fever complex. Metaphorically speaking, the eczema–asthma–hay fever personality is born dyed in the wool, and the tension personality is born wool and is dyed in the vats of life experience.

THE SEXUAL FACTOR IN THE TENSION AND ECZEMA–ASTHMA–HAY FEVER PERSONALITIES

Personally I find difficulty in evaluating causal roles here, because sexual tension is at one time or another so universal an element in human experience that it loses specific significance. Undoubtedly one meets, as did Klaber and Wittkower,[8] Pearson and earlier investigators from the time of Jacquet and Sack,[41] examples of "week-end rosacea," of extensive neurodermatitis on sex conflict backgrounds [42] and of urticaria of similar causation. It cannot be denied, however, that some of the correlation of sexual data is effect, not cause, and that it results from the discovery, sometimes only half conscious, that the scratching of an itch furnishes a fair substitute for sexual orgasm and a corresponding release of emotional and nervous tension when carried to a finish. Klauder [20a] stated the opinion that outright sexual psychoneuroses play a relatively small part in the causal machinery of neurodermatitis. In the eczema–asthma–hay fever patient, the nocturnal itching bout and the practice of wrist-grinding, terminating in profuse sweating with exhaustion, relaxation and sleep out of all proportion to the muscular effort involved, suggest the operation or complication of a sexual factor, if it be only unconscious cutaneous masturbation. In the vulvar and scrotal lichenifying eczemas and in the intertriginous streptomycoses in which emotional sweating is the prelude to an attack, it is possible occasionally to see the beading of the apocrine sweat gland areas with sweat as a sexual problem or situation is discussed. As such sweating furnishes soil for infection, such dermatoses may be said perhaps to have a sexual dermatoneurosis in their background. I have even seen a dyshydrotic-dermatophytic-pyogenic eruption on the hands of a maladjusted wife, which flared up at her husband's week-end disturbing demands, finally clear by conferences in which both parties were reeducated to an adequate sexual adjustment (see also Pearson [5]). Thus

41. Sack, W. T.: Psyche und Haut, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, vol. 4, pt. 2, p. 1302.

42. Stokes, J. H.: The Effect on the Skin of Emotional and Nervous States: II. Masochism and Other Sex Complexes in the Background of Neurogenous Dermatitis, Arch. Dermat. & Syph. **22**:803 (Nov.) 1930.

the emotional background and conflicts of sex are capable, as are many other fields and types of emotional conflict, of providing the bases for a train of infection-allergic phenomena leading to what would not ordinarily be regarded as neurodermatitis. The tension personality—I-sensitive, conscientious and fearful of inadequacy—makes a specially favorable soil, perhaps, for such sex-linked psychogenous mechanisms.

SUGGESTIONS FOR DIAGNOSIS AND TREATMENT

While the diagnosis and treatment are not, strictly speaking, a part of the assigned scope of this paper and have been discussed by me more broadly elsewhere,[33] a brief résumé of a technic of procedure may provide the chance for hearers to approve or damn some of these concepts. Let it be reemphasized that in a psychoneurogenous condition one is dealing with a factor, not a sole cause, in the overwhelming majority of cases of the types I have discussed and that a careful analysis is the essential preliminary, with correction of the principal pathogenic components, including the allergic state, if a result is to be complete or lasting. First of all, the physician should practice the objective recognition of tension parallel with, if not a bit ahead of, the anamnestic approach. When there is not time or skill for the latter, the former may at least identify the state of the patient. At the first and subsequent sessions the grade of color play (flush reactions) of the face and neck, the hands and feet and the areas involved by the lesions should be studied. This includes the stasis, flush and rate of paling of the dependent and elevated extremity,[43] a fair index of vascular tone. Weight should be given to the color play of the rosacea area, but I am unwilling to say that I have found it a reliable guide to specific elements in the patient's life and thought. That is, if the mention of "husband" or "wife" brings on a color change, this does not mean trouble at home. The high supraclavicular flush suggests the "vagotonic." Other signs are rapid blinking, suffusion of the eyes, tremor of the mouth and chin, the "washboard forehead" (in which the eyebrows are drawn up into the hair—not the frown in which the hair is pulled down into the brows) and the elevated timbre and needless assertive loudness of the voice or, contrariwise, the subdued monotone. The "motor snap" with shoelaces, tie and coat and sitting forward in the office chair are signs in patients too well bred to fidget, wring their hands, drum, sketch or tap their feet. Sweat on the hands, on the examining table sheet or at the site of flexural lesions during examination may have meaning. Such signs as the rigid posture on the table, the out-thrust feet, lying on one hip with the knee drawn up and widely dilating pupils during examina-

43. Stokes, J. H., in discussion on Landis, E. M.: The Capillaries of the Skin: A Review, J. Invest. Dermat. **1**:295, 1938.

tion of the torso are often as useful as the commonplaces of exhibitionism and the bedroom eye. Above all, the dermatoneuropsychiatrist must learn to recognize the poker face [33a]—the mask of the patient with neurodermatitis or the eczema–asthma–hay fever personality, in which two peering and birdlike or clouded and darkly noncommittal eyes gaze with almost embarrassing directness straight at the observer, from between motionless lids set in an impassive face. The prognosis of the patient with the poker face is far more qualified than that of the patient who flushes, blinks, trembles or wrinkles. And the prospects for a successful outcome of an office catharsis and identification of a simple conflict with recovery on rest, reassurance and adjustment are least in them.

It is hardly to be expected that the busy specialist will wish to apply even the simpler methods of office analysis by leads and catharsis described in my previous paper. It is possible, however, to draw up a species of general prescription for the psychoneurogenous phase of the eczema–asthma–hay fever person's difficulties and a similar set for those of the tension personality, and this I do in full awareness of the risk I run in offering ready-made solutions for such complex problems.

Basic Psychotherapy of the Eczema–Asthma–Hay–Fever Patient

A. For the Infant and Prepuberal Child:

1. Supervised play with other children under child guidance and nursery school direction.

2. Calling off of the oversolicitous and overprotective parent.

3. Treatment of the child as an equal, with explanation, patience, laissez faire and persuasion replacing to varying degrees parental sovereignty, severity, repression, irritability and "don'ting."

4. Elimination of as many contacts as possible with the irritating ("electric") or irritable and repressive parent or other personality (in school or away from home).

5. Adjustment of marital and personality conflicts between parents and insecurity-producing discriminations among children in the family as promptly and as early in life (even prenatally) as possible.

6. Discouragement of the forcing tactics, marks standards and competitive technics of teachers, schools and sports.

7. An attempt to conserve rest; not too many visitors, not too much excitement, the midday quiet period, if not nap, and the combating of night life and overstudy.

8. Facilities for discharge of tension, noncompetitive sport and exercise, outdoor life and nature study. The person with the eczema–asthma–hay fever complex is a radically different being in the open.

9. Training in self confidence and self reliance (exploration, experiment, trips alone, direct relations with teachers, advisers and physicians, not mediated through the parent, and systematic but not exaggerated encouragement).

B. For the Adult:

1. Not too much explanation of the mechanism which characterizes or creates the mental state, at least not to the more unstable subjects.

2. An attempt in suitable cases to manage the parent problem as in the child, but more circumspectly.

3. An effort to identify in simple conversations on current activities of the patient, his plans and problems, the more obvious conflict factors and especially the critical inferiorities which in crisis form can precipitate asthmatic and neurodermatitic explosions.

4. Education as to I-sensitiveness, kinetic drive and effect of competition, in one or two simple talks.

5. Systematic encouragement combined with emphasis on self acceptance and depersonalization of outlook.

6. An arbitrary prescription of rest, with reduction in scholastic, extracurricular, sport and social tension activities by 35 to 50 per cent until improvement takes place. Permanent reductions in scale of attempted activity and achievement.

7. Training in the technic of relaxation.

8. Training in discharge of tension via the long muscles, especially walking (cross country preferred) from one to four hours daily, with mind on the present, without thought of past or future and without time schedule or destination. This is to be supplemented by a manual hobby and an outdoor noncompetitive sport, such as rowing, canoeing, swimming, sailing, skiing or skating—not driving a car, which is a "poisonous joy" for persons of this kind.

9. Change of scene (i. e., adjustment by flight) only in critical and unmanageable situations.

Basic Psychotherapy of the Patient with the Tension Personality

1. A talk on general principles in which the fundamental nature of tension is explained, with its relation to behavior of the skin.

2. The attack on the obligatory in repeated sessions by the injunction *not to do* whatever gives the patient a feeling that it *must be done.*

3. Cutting off access of the "must" influences to the patient (in severe cases, no mail, no answering of telephone, no making or carrying out of engagements, no acceptance of new social obligations and a repudiation of up to 50 per cent of current social commitments).

4. Provision of physical sanctuary (i. e., own work-room or garden) to be used for a set period each day.

5. A lecture on the "don't give a damn" attitude—or temporarily conscienceless attitude—illuminated by such slogans as "a hundred years from now. . ."

6. Drill in relaxation, both systematized, as in exercises, and waiting with patience, as in doctors' offices or for traffic lights, substituting shrugs for jaw clenching and nail gnawing.

7. Provision for discharge of tension by noncompetitive physical means (notably again, walking), manual hobbies and stopping of competitive sport and "exercise."

8. An arbitrary rest prescription based on the preceding elements, usually a one hour nap or a nap plus relaxation (with perhaps graded sun bathing), followed if possible by one hour of a hobby, in sanctuary.

9. Conversational exploration of simpler conflicts (often part of the history taking), with suggestions for adjustment.

10. Systematic practice in living for the moment and viewing life with serene detachment (the "big and little Mary" device helps).

11. Systematic encouragement, with practice in self esteem and self acceptance.

12. Education of the patient in the recognition of his own signs of tension, including watching his own voice, hand, eye and forehead, and in the application of remedies.

It will be noted that I have not discussed physical therapy, thalamic sedatives, administration of calcium and atropine, all valuable aids though they are. I have said little of the uses and disuses of the allergic work-up. I have discussed elsewhere [33b] but not in this paper the ichthyotic or xerodermic factors, the pyogen and fungus susceptibilities, the focal infective and the metabolic elements in a neurodermatitic picture. I have not said that the psychogenous cause is the sole cause or that the personality is the entire picture, and I have not offered to cure the patient by psychotherapy alone.

ABSTRACT OF DISCUSSION

Dr. Harry C. Solomon, Boston: It is agreed off-hand, I suppose, that the emotional state will cause common conditions, such as flushing and sweating. This is well illustrated in Raynaud's disease. An injection of epinephrine in a person with Raynaud's disease causes Raynaud's syndrome. Exactly the same state can be produced by causing an emotional shock in that patient, and it can be shown by the vascular conditions in the periphery of the skin. All that may be important and make beautiful research divisions, but the great problem when one is confronted with the patient is treatment. The treatment may be dependent on what is learned from the various factors. It may be based on a question of physical fitness, such as some dietary restriction, or it may also be based on a question of the personality, such as reducing the amount of tension or clearing up some of the underlying difficulties that the patient is unable to handle in a normal, well integrated manner. All those considerations come into the problem of treatment of any dermatitis.

It is interesting that the two most conservative parts of the world, Philadelphia and Boston, have been willing to start off in attempts to make these studies. Dr. Stokes has told you of the Philadelphia work. In Boston, particularly at the Massachusetts General Hospital, there has been going on for a year and a half a study from a psychiatric angle of dermatologic cases, loaned or given by Dr. Lane. These patients have been taken into the psychiatric ward, some of them for as long as four months, so that the effects, particularly in those with atrophic dermatitis, might be studied. The investigators have been able to show that with certain types of psychotherapeutic care the patient seems to improve but that confronting the improved patient with certain problems which he has not been able to handle well—which he is said to be sensitive to—causes an immediate breakdown of the good results and a recurrence of the dermatitis.

All that one can emphasize at this moment is the importance of the psychologic approach both from the standpoint of what can be done therapeutically and in the way of further understanding and elucidation. The important thing to bear in mind is that it is not a single approach that is wanted. It is a matter of a correlation of the personality factors on the psychologic level with the physiologic levels, an understanding of the central nervous system and the central controls, an understanding of the skin—the synthesis of a coherent whole, with the psychiatrists on one hand in the picture, perhaps, and the dermatologist and the physiologist on the other. Correlation and understanding of the total reactions of the personality of these emotional factors, some hereditarily conceived and some acquired in the fight of life, are needed.

Dr. Eugene T. Bernstein, New York: I am grateful to Dr. Stokes for stimulating new concepts of the interrelation of psychic, including emotional, processes, and somatic processes, which are gradually entering into the domain of dermatologic research.

When Socrates came home from army service, he reported to his Greek countrymen that in one respect the barbarian Thracians were in advance of the Greek civilization, because they knew that the body cannot be cured without treating the mind. Therefore, he continued, many diseases are unknown to the physicians of Hellas because they are ignorant of the "whole."

At present a new chapter is opening, a chapter of psychobiology in which the total personality is considered, not the cutaneous organ separately. The importance of the "whole" is being recognized through all phases of this psychobiologic study. To understand the "whole," one has to study the parts with a new emphasis on the "whole."

In a recent paper Carrel stated that one cannot understand the behavior of a single cell apart from its time and space environment, because the cell reflects some minimal quality of sensation of pain or pleasure; even in processes of elimination and assimilation of chemical substances there is realized some quality of painful or pleasurable sensation.

In a discussion of my recent paper on this subject, Dr. Manfred Sakel emphasized his observations as identical to mine. Our observations indicate that insulin shock in many instances cures cutaneous conditions in patients with schizophrenia. This is most frequently true in cases in which the condition is recalcitrant and resists every therapeutic measure previously found in the curative armamentarium of dermatology. It is difficult to understand the mechanism by which insulin simultaneously effects recovery of a mental state coincident with a complete cure of the accompanying cutaneous condition hitherto regarded as incurable. This may be due to the fact that the cutaneous organ and the central nervous system develop from the same germinal layer, the ectoderm. Both systems are ontogenetically and teleologically closely related.

Dr. Henry D. Niles, New York: One of the greatest contributions of the many Dr. Stokes has made to dermatology is the attention he has drawn toward the role of emotions and mental states in the production and aggravation of dermatoses. It is interesting that one person may have either at the same time or at different times one or two or more of the dermatoses that are considered to be of neurogenic origin, besides the ones that have been mentioned, such as neurodermatitis and eczema of various forms. These include alopecia areata, canities, vitiligo, herpes simplex, herpes zoster, herpes progenitalis, neurodermatitis, lichen chronicus simplex circumscriptus of Vidal, angioneurotic edema,

urticaria (especially the factitial type), rosacea, lichen planus, pompholyx, hyperhidrosis, nummular eczema, pruritus ani and pruritus vulvae. In this group one must also include acne excoriée des jeunes filles of Brocq. This condition may be regarded as a compulsion neurosis. Many of these patients admit that they feel "compelled" to dig out secretions of sebum and pus and to scratch any small elevation to a level with the normal skin.

Although this condition occurs in patients of the acne age and on the same areas as acne vulgaris, it is not true acne, as evidenced by the lack of comedos. It is important to differentiate it from acne vulgaris, as naturally it does not improve with roentgen ray therapy, and I have seen some of these patients with roentgen dermatitis as a result of prolonged irradiation.

Psoriasis may in some patients occur only after nervous or emotional strain. Rosacea, pruritus ani, pruritus vulvae and the circumscribed form of neurodermatitis are frequently associated with nervous disturbances at the time of the menopause. Disseminated neurodermatitis is most often seen in high-strung, young, tall, thin persons. Most of these are students, and their eruption is worst just before examinations and greatly improves during the summer vacation when they are free from nervous strain. I have seen patients in whom herpes progenitalis was apparently caused by fear of infection or sense of guilt following illicit intercourse. Herpes zoster often follows fatigue or nervous shock. It is known that in some cases warts can be cured by suggestion; I believe that some warts apparently are produced by psychic factors.

I should like to mention 3 cases which I have encountered in private practice which are illustrative, I think, of the role emotions play in dermatoses.

Case 1.—Nummular eczema of the hands was present in a girl seen for several years. The lesions always disappeared in the summer until one year when she went to summer school and had no rest. The patient was ambitious and high strung.

Case 2.—Pruritus ani developed in a young man. He graduated from a university and wanted to go to medical school but was unable to do so because of finances. He could not find a good job and, in fact, had to end up as a dishwasher. He had feelings of inadequacy, which manifested themselves as pruritus ani. This had been treated as a fungous eruption by many physicians, with resulting dermatitis from fungicidal applications. His pruritus disappeared entirely by "laying the cards on the table" before him, convincing him what the basis of his pruritus was and giving him only mild applications. He has remained well since then.

Case 3.—A woman had chronic urticaria which was resistant to all treatment but which disappeared shortly after her husband's death. He had had diabetic gangrene, and she was confined taking care of him.

Dr. S. William Becker, Chicago: One of my students recently asked what I thought was an intelligent question, namely, why it is that physicians in every other branch of medicine recognize functional disease but the dermatologists do not recognize it at all. The statements made by Dr. Stokes apply to all cutaneous and even other functional diseases. He has picked out perhaps the most severe example. It is one of the most common cutaneous disorders, and it has a distinct hereditary tendency. Moreover, patients with this condition are driven to desperation by the pruritus, which interferes with their sleep and accentuates their exhaustion, and by their failure to obtain relief by orthodox methods of treatment.

Other functional cutaneous diseases when they are severe, I believe, are associated with the same neuropsychiatric difficulties. If they are pruritic, such as severe dermatitis herpetiformis, I do not believe that there is a great deal of difference either in the makeup of the patient or in any of the collateral factors. Pruritus ani I should put in the same group. If they are not pruritic, the vicious cycle is not so prominent, because then the patients do not lose sleep on account of tremendous itching. However, as patients have been studied with the severe functional diseases, namely, those that appear in childhood—such as alopecia areata, which usually goes on to alopecia totalis—we have found the makeup of the patient, the tension frame of mind and the energy drive are all there, with the allergies not so prominent.

I believe that functional disease represents perverted fatigue. Here is a person who actually works harder than the average person, so that he undoubtedly has a larger amount of the products of exhaustion in the body, but he has a lesser sense of fatigue. The easiest way to get the cooperation of the patient is to emphasize the fact that he is overworked, that he is more exhausted but has less sense of fatigue and therefore that he must change his ways.

I was glad to see Dr. Solomon include a neurologic aspect along with the psychologic. I believe that the term "neurosomatic" should be used rather than "psychosomatic." I am not so pessimistic regarding the prognosis of these patients. If they are treated early in life and if the cooperation of the patient and the family can be obtained, I believe that most of them can be relieved.

Dr. Samuel Ayres Jr., Los Angeles: The dermatologists are indebted to Dr. Stokes for calling attention to the factors of the mind and functional disturbances in dermatologic conditions, but the question comes to my mind as to what is cause and what is effect. I think, particularly in the field of dermatology, that an adequate system of controls must be maintained. Given a person who has been pestered since infancy with eczema, asthma or hay fever and assuming that the cause may be some organic factor and not a functional factor, there unquestionably would be changes in personality. It would be interesting as a control series to see what the psychic reactions and factors are, for instance, in a group of persons afflicted with some long-continued infectious disorder of known etiology, such as Norwegian scabies or tuberculosis, that might have persisted for years.

One of my colleagues maintains what he calls a desert health school situated about twenty miles from Los Angeles up in the mountains in the desert, where he takes children with asthma and hay fever who are unable to attend the public schools. Without any other psychic factors than putting these children in a different climatic environment, they gain weight, change their personalities and are able to live normal lives. Some would argue that it is taking them away from their home environment and putting them in this school that does it, but it seems more likely that it is the difference in the climatic factors or other environmental factors. I suspect that the home factors are not the only ones involved.

Dr. Joseph V. Klauder, Philadelphia: I should like to discuss one phase of psychosomatic relation to cutaneous diseases. Properly speaking, one cannot label a cutaneous disease psychogenic, since there are no features indicative of psychogenesis. What evidence justifies the conclusion that pruritus, for example, is a psychosomatic symptom? I do not challenge psychosomatic relations in cutaneous medicine, since I first endeavored some years ago to emphasize its importance in the practice of the dermatologist (Cutaneous Neuroses, *J. A. M. A.* **85**:1683-1689 [Nov. 28] 1925).

The application of the term "psychogenic" to diseases of the skin I do not regard as based entirely on a post hoc conclusion. In a study of the psychogenesis of diseases of the skin, the occurrence of various cutaneous reactions and, indeed, of cutaneous diseases following suggestion in hypnosis comes close to fulfilling the principle of inductive reasoning "The same cause under the same circumstance produces the same effect."

The stigmas of the crucifixion I regard as additional evidence. The cutaneous lesions that characterize the stigmas appear as a somatic representation of psychic events, intimately, if not exclusively related to religious ecstasy as I have pointed out elsewhere (Stigmatization, ARCH. DERMAT. & SYPH. **37**:650-659 [April] 1938). In this regard the tremendous nature of the stimulus and the intense mental makeup of stigmatists should be recalled.

More recently in studies sponsored by the National Research Council (Conference on Experimental Neuroses and Allied Problems, Washington, D. C., National Research Council, 1937), symptoms of neurosis have been experimentally produced in a variety of animals. Briefly these symptoms are produced by confusion in the production of a conditioned reflex. Perhaps a clinical correlation of these experiments may be envisaged by substituting conflict for confusion. Although psychosomatic reactions such as pruritus and urticaria have not been experimentally produced in animals, veterinarians tell me that in some instances pruritus in dogs appears to have a psychoneurogenic basis.

DR. MARION B. SULZBERGER, New York: Dr. Stokes's paper and Dr. Solomon's discussion point out that in human beings there is no such thing as a brain standing alone, swimming around in the atmosphere without any connection with the soma, and also that there is, on the other hand, no such thing as somatic tissues isolated from the psyche and without some form of innervation. Disease has to be considered from the viewpoint of treating both the immediate organ separately as well as one can and also everything which contributes to the disease of that organ. There is really only one point on which I have to take issue with the emphasis or the accent of this contribution. There is perhaps nothing more ancient than the concept that psychic and emotional factors influence disease. There is nothing older than the concept that constitutional, hereditary factors or the choleric, lethargic, lymphatic and sanguinous constitutions or personalities are of importance in disease, and particularly in this group of diseases.

It is true that Socrates mentioned this concept, and it was mentioned long before Socrates' time. In dermatology, the very names which have been applied to these diseases prove amply that the older concepts were those which attached the most importance to the psyche and the nervous factor, for example, *nevrodermite* or *neurodermite* of Brocq and *mnemodermie* of Jacquet, the concept of dyshidrosis with its connotation of a nervous element influencing the sweat secretions. Just as the "nervous" concept is really the oldest concept, so also are the therapeutic approaches along psychic lines the oldest.

To tell the patient to rest, to stop work, to go to a beach, to give up his business, to get out of his family environment, that he has nothing the matter with him that a million dollars will not cure: those are the older approaches.

The idea that herpes simplex appears after an emotional upset, after extramarital intercourse or at the time of the menses is an old and a true concept.

I have been continually buffeted between my good friends Dr. Stokes and Dr. Becker on the one side and Dr. Coca and Dr. Walzer on the other. One group has laid emphasis on the psychoneurogenic aspect, and the other group on the exposure to allergens. In my opinion both viewpoints are important, but the importance

of the psychoneurogenic concept has long been emphasized and long recognized, while the concept of allergens and specific hypersensitivity is newer and has promise of being more fruitful.

The new contribution is that these patients are hypersensitive to certain substances and that there are definite eliciting agents in these diseases. What produced a herpetic reaction was under the older concept only the psyche or the emotions; but the important new contribution is that there is a culturable, filtrable virus there which can be isolated from the lesions. The important new contribution about dyshidrosis is that when sweating occurs, fungi begin to act, or the leather begins to produce reactions on the feet, or the dyes create allergic reactions—in other words, what seemed to be a purely neuropsychogenic state was really elicited by exposure to fungi or to leather or to a dyed garment or to a medicine which had been taken internally. These are the new aspects; the other, psychogenic, theories are the older ones.

Now what about the therapeutic approaches based on these two approaches? The oldest therapeutic approaches were, for example, exorcising of spirit, suggestion and hypnosis. Thirty to forty years ago most of these patients at one time or another were hypnotized or mesmerized, or were treated by the Dubois method of relaxation. These approaches were not, in general, sufficiently satisfactory, and entailed many disagreeable elements and drawbacks and dangers, so that medicine was forced to advance and to study new approaches to this group of diseases. Undoubtedly, the greatest modern advance was made when these diseases were in many instances shown to be in some way connected with the immunologic phenomena of specific sensitization.

Every good physician knows that these patients must be treated from every angle. The new way of approach—the additional feature that modern medicine has taught—is that it must be realized that in many of these cases one has to look for living and nonliving agents and allergens, as well as to try to relieve the patient of strain and stress.

Dr. John H. Stokes, Philadelphia: I am appreciative of Dr. Solomon's consideration in coming before us, because I am always timid about this stuff. When I sent this paper to Dr. Solomon, he said, "Why take this controversial tone about the whole thing? Everybody accepts the fact nowadays that psychosomatic factors are important. Why talk as if your audience refused to believe anything of the sort?"

I did not write back and say, "You don't know dermatologists." There are reasons why the dermatologist finds it difficult to accept the psychosomatic. He likes to distinguish between what is tangible and what is intangible. The tradition of the dermatologist who can see and touch and apply a lens is against the acceptance of such conditions as a flush or an expression, which pass fleetingly across the face. I am glad the dermatologist is a little stodgy toward the subject, because nothing will bring the overenthusiastic dermatoneuropsychiatrist, so to speak, to book like dermatologists' determination to see a series of normal persons, which, by the way, does exist. In fact, there are several series of normal persons. I am glad too that attention was directed to the cart-horse relation, but it must be remembered that the situation is like the vicious circle, for instance, when a pinwheel is spinning, deciding which part is black and which white is difficult.

I think the emphasis placed by Dr. Niles and Dr. Becker on the rest factor is extremely important. If you will watch these children from infancy, as I have had occasion to do now for fifteen years, you will realize how early in life this rest deficit begins.

PARENTERAL USE OF HYPERTONIC DEXTROSE FOR RELIEF OF PRURITUS AND OF SERUM SICKNESS

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AND
ROBERT J. KOSITCHEK, M.D.
LOS ANGELES

The purpose of this report is to present observations on the therapeutic effect of hypertonic solution of dextrose in patients with serum sickness and with certain types of pruritus. It was observed that a 5 per cent solution of dextrose given by hypodermoclysis relieved the itching of a patient with exfoliative dermatitis of unknown cause. After this experience, it was decided to try the effects of parenteral administration of a hypertonic solution of dextrose, purely on an empiric basis, on patients with other pruritic diseases. We recognize that great care must be exercised in the evaluation of the treatment of subjective symptoms, such as pruritus, but feel that our observations have shown a certain consistency and have been sufficiently controlled to represent reliable material. In some of the cases objective signs, i. e. urticaria, have responded parallel with the subjective manifestations. We have not been able to establish the theoretic bases for these results.

CLINICAL RESULTS

During the early part of the study a 5 per cent solution of dextrose was used subcutaneously. It was found later that the intravenous route was more efficacious. The usual procedure was to administer 50 cc. of a 50 per cent solution of dextrose and follow this, when indicated, with a repetition of the same procedure or with the administration of larger quantities of 5 or 10 per cent solutions of dextrose. We did not observe that the rate of injection or the temperature of the solution had any appreciable effect on the results. In several instances the effects were so instantaneous as to suggest a psychic effect. This factor was ruled out by the fact that saline solution administered in the same manner had no effect in 15 control cases.

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Our series comprises 58 patients [1] who presented pruritus as an outstanding symptom. Of these, 43 were satisfactorily relieved, and no results were obtained in 15. Of the 43 who responded satisfactorily, 10 had serum sickness, 7 pityriasis rosea with severe pruritus, 4 pruritus ani, 3 pruritus vulvae, 3 generalized urticaria, 3 dermatitis medicamentosa, 3 generalized exfoliative dermatitis, 2 generalized seborrheic dermatitis and 1 each, generalized lichen planus, pruritic papular secondary syphilis, keratoderma climactericum, neoplastic obstructive jaundice, lymphoblastoma cutis, vegetative pemphigus, dermatitis herpetiformis and generalized erythema multiforme.

Of the 15 who failed to respond to this treatment, 5 had infectious eczematoid dermatitis, 4 poison oak dermatitis, 5 senile pruritus, 1 pruritus vulvae, 1 generalized seborrheic dermatitis and 1 atopic eczema associated with asthma.

Three of these patients were treated with a 5 per cent solution of dextrose by hypodermoclysis; the remainder were given 50 cc. of a 50 per cent solution of dextrose intravenously, and in 7 this was immediately followed by 1,000 cc. of a 10 per cent solution of dextrose intravenously. Of the 58 patients, 15 were used as controls. In 11 of the controls 50 cc. of isotonic saline solution was given intravenously as the initial treatment. Neither objective nor subjective relief was obtained. At intervals varying from one-half to several hours after the saline solution was given, dextrose was administered, with immediate results. In 4 cases in which itching had been a prolonged symptom, as in obstructive jaundice, lichen planus and persistent pityriasis rosea, and in which periodic injections of dextrose kept the pruritus well under control, substitution of saline solution without the knowledge of the patient inevitably demonstrated that the solution of dextrose produced relief and the saline solution did not.

The most noteworthy results were obtained in 10 patients with serum sickness. Three of them had previously failed to respond to intensive treatment with epinephrine and calcium gluconate. In the 10 patients the results were immediate, consistent and complete, not only in relief of pruritus but in relief of the accompanying pains in the joints, urticaria and fever. This method of treatment has been used in many cases of serum sickness in other services of the Los Angeles County Hospital with success. However, those not under our observation are not included in this report.

REPORT OF CASES

CASE 1.—A 26 year old Negress had severe generalized exudative and exfoliative dermatitis of three weeks' duration. One week previous to the appearance of the dermatitis she had received three extravenous injections of staphylococcus vaccine

1. Seven of these patients are included from the private practice of Dr. C. Russell Anderson.

for a mild furunculosis. Shortly after the last injection a generalized pruritus developed, for which she applied several irritating ointments.

Physical examination revealed a generalized exudative and exfoliative dermatitis with evidence of extensive excoriations. There was considerable edema of both the upper and the lower extremities. She was given 1,000 cc. of a 2.5 per cent solution of dextrose by hypodermoclysis, and the itching disappeared within fifteen minutes after the injection was started. One hour later 1,000 cc. of a 5 per cent solution of dextrose was given by hypodermoclysis, and the pruritus did not return until twelve hours later.

The patient was relieved of her itching for the next eight days by the daily subcutaneous injection of 1,000 cc. of a 5 per cent solution of dextrose. After this, we gave daily 1,000 cc. of a 10 per cent solution of dextrose intravenously for

Patients with Pruritus and Serum Sickness Treated with Hypertonic Solution of Dextrose

Diagnosis	No. of Patients	Result
Serum sickness	10	Complete relief of signs and symptoms
Pityriasis rosea	7	Relief of itching for variable lengths of time
Pruritus ani	4	Relief of itching for variable lengths of time
Pruritus vulvae	3	Relief of itching for variable lengths of time
Urticaria	3	Relief of itching for variable lengths of time
Dermatitis medicamentosa	3	Relief of itching for variable lengths of time
Exfoliative dermatitis	3	Relief of itching for variable lengths of time
Generalized seborrheic dermatitis	2	Relief of itching for variable lengths of time
Generalized lichen planus	1	Relief of itching
Papular secondary syphilis	1	Relief of itching
Keratoderma climactericum	1	Relief of itching
Neoplastic obstructive jaundice	1	Relief for three day periods
Lymphoblastoma cutis	1	Relief of itching
Vegetative pemphigus	1	Relief of itching for 12 hour periods
Dermatitis herpetiformis	1	Relief of itching for two hours to two days
Generalized erythema multiforme	1	Relief of itching for one hour to two days
Infectious eczematoid dermatitis	5	No relief
Senile pruritus	5	No relief
Rhus dermatitis	4	No relief
Atopic eczema with asthma	1	No relief

four days. The patient was observed for three more days and was then discharged as cured. This case aroused our interest in the use of dextrose in treating patients with severe pruritus.

CASE 2.—A 22 year old white woman received 3,000 units of tetanus antitoxin five days before admission to the hospital. Epinephrine, administered on four occasions, gave only temporary relief, and the patient was admitted in a hysterical condition with urticaria, excoriations and generalized adenopathy. Two attendants were needed to restrain her. She had not received epinephrine for four hours at the time of admission.

The patient was immediately given 50 cc. of a 50 per cent solution of dextrose and was sound asleep within five minutes after the injection. The urticaria had disappeared within fifteen minutes, but it reappeared within two hours. Two thousand cubic centimeters of 10 per cent dextrose in saline solution was given within the next seven hours, and the patient remained entirely asymptomatic and free from urticaria. The patient had no recurrence of symptoms and was discharged three days later.

CASE 3.—A 20 year old white man had been given 3,000 units of tetanus antitoxin five days before admission. He was considered to be in an emergency condition because of severe generalized pains in the joints, generalized adenopathy, tachycardia and an oral temperature of 103 F.

While he was receiving 50 cc. of a 50 per cent solution of dextrose intravenously, the pains in the joints completely disappeared, and the patient became asymptomatic. One thousand cubic centimeters of a 10 per cent solution of dextrose was given, and within four hours the temperature had dropped to normal limits. There was no recurrence of symptoms. The patient was discharged two days later.

CASE 4.—A 3 year old white girl entered the hospital with a generalized rash, associated with severe itching and urinary frequency of five days' duration. The patient had been given phenobarbital for nervousness for a month. Administration of the drug had been discontinued with the appearance of the rash. Dermatitis medicamentosa was the diagnosis made on entry. On admission the child was crying furiously and digging at the urticarial lesions which covered her body. She constantly called for the bed pan and had a urinary frequency of every fifteen minutes. Her vaginal and urethral orifices were red, with many excoriations. The urine was normal.

She was immediately given 30 cc. of a 50 per cent solution of dextrose intravenously and 200 cc. of 2.5 per cent dextrose in saline solution by hypodermoclysis. The patient was free from the "itchy" sensation within twenty minutes after treatment had been started, and at no time during the next four days of hospitalization did she complain of pruritus or scratch herself. She did not urinate or ask for the bed pan from the time of starting the treatment, 7 p. m., until morning. The treatment was repeated in the morning, and the patient was discharged as satisfactorily cured three days later.

CASE 5.—The patient was a 20 year old Mexican woman in whom a generalized urticaria developed following a debauch with chocolate candy. The urticaria was present two days before admission and was not relieved by epinephrine. She was admitted as in an emergency condition owing to the severe pruritus. The patient was relieved of her itching by the injection of 50 cc. of a 50 per cent solution of dextrose. The urticaria reoccurred after a twenty-four hour interval and at this time was not alleviated by the intravenous injection of 50 cc. of physiologic solution of sodium chloride. One hour later 50 cc. of a 50 per cent solution of dextrose was injected, with immediate and permanent relief.

CASE 6.—A deeply jaundiced 64 year old white man with a proved diagnosis of carcinoma of the head of the pancreas had suffered from intractable pruritus for approximately three months. His icteric index ranged between 80 and 133. All types of therapy had failed to relieve the itching, and heavy sedation was being employed.

For the past three months this patient has received 50 cc. of a 50 per cent solution of dextrose at three day intervals. This has enabled the patient to live comfortably, without the aid of any other form of treatment. On four occasions 50 cc. of physiologic solution of sodium chloride was substituted for the dextrose solution, and no relief was obtained.

CASE 7.—A white man aged 56 had been suffering from severe itching around the anus and scrotum for sixteen years. Examination revealed large anal and scrotal excoriations.

The patient had been treated by various physicians during this time, without success. He was then given 50 cc. of a 50 per cent solution of dextrose on three successive days, and he became asymptomatic. Each injection relieved the itching for longer periods, and ten days elapsed before its return after the third injection. The irritative lesions healed within two weeks. The patient now receives one injection every ten days and has been entirely free of symptoms for two months.

CASE 8.—A 20 year old Mexican had generalized erythema multiforme and subsequent exfoliation, associated with episodes of severe pruritus which would last for several hours at a time. Local applications partially relieved the pruritus during the day, but at night even large doses of sedative drugs could not prevent the itching from keeping the patient awake.

Fifty cubic centimeters of a 50 per cent solution of dextrose relieved the patient for approximately six hours on many occasions during six weeks of hospitalization. Fifty cubic centimeters of physiologic solution of sodium chloride produced no relief, while the dextrose solution was always successful in alleviating the pruritus, permitting sleep without sedation.

CASE 9.—A 27 year old white man had papular pityriasis rosea with pruritus of three weeks' duration, which was not relieved by local application.

Fifty cubic centimeters of physiologic solution of sodium chloride did not relieve the pruritus. Fifty cubic centimeters of a 50 per cent solution of dextrose relieved the severe itching within ten minutes. The pruritus returned the following morning and was permanently relieved by the readministration of hypertonic solution of dextrose, although the cutaneous lesions were present for a week longer.

CASE 10.—A 55 year old white man had extensive infectious eczematoid dermatitis of two months' duration.

Fifty cubic centimeters of a 50 per cent solution of dextrose was given intravenously on four different occasions, but the pruritus was not relieved.

CASE 11.—An 18 year old white man had generalized vesicular dermatitis venenata due to contact with poison oak. Fifty cubic centimeters of a 50 per cent solution of dextrose was immediately given on hospitalization, without producing relief from the pruritus. The injection was repeated four hours later and again failed.

COMMENT

The presented material is offered on a purely empiric basis. We have not attempted to establish the rationale of the procedure and realize that there are many implied inconsistencies and paradoxes in the light of current knowledge of carbohydrate metabolism. In a small number of patients whose blood sugar levels were studied during (*a*) the period of pruritus before administration of dextrose, (*b*) the period of relief following administration of dextrose and (*c*) the return of pruritus, no correlation could be determined. This group, however, is so small that it does not permit conclusions except recognition of the simple observable fact that the rise in blood sugar itself is not responsible for the relief of the pruritus, since a comparable rise is obtained in unrelieved patients. The possibility that the phenomenon is based on a physical osmotic effect must be considered.

CONCLUSIONS

The intravenous administration of hypertonic solution of dextrose (*a*) is of value in the treatment of serum sickness, (*b*) is of temporary but often prolonged value in the treatment of certain kinds of pruritus and (*c*) has failed to alleviate pruritus in patients with dermatitis venenata, senile pruritus and infectious eczematoid dermatitis.

SENSITIZATION TO ARSENICAL COMPOUNDS

SENSITIZATION TO A PENTAVALENT ARSENICAL FOLLOWING USE OF A TRIVALENT ARSENICAL

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Reviewing the literature on sensitivity to arsenical drugs, we found only 3 cases of sensitivity to both trivalent and pentavalent arsenicals. Two cases were reported by Epstein [1] and the third by Golz.[2] In view of the rarity of hypersensitivity to both of these types of drugs, the following cases are presented. In these cases an exfoliative dermatitis developed on the administration of neoarsphenamine, and the eruption recurred after injections of tryparsamide.

REPORT OF CASES

CASE 1.—Mrs. L. A., aged 40, born in the United States, registered in the dermatologic clinic of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Sept. 9, 1939, seeking treatment for a generalized eruption. She gave a history of "ulcer" in 1936 and of a miscarriage in 1924. For the previous two years she had been receiving from her private physician antisyphilitic treatment, consisting of administration of a bismuth compound and neoarsphenamine.

For two months prior to registration at this clinic, she complained of generalized itching. This was followed by a generalized eruption, which consisted of intense erythema, exfoliation and edema. The greatest involvement was on the face, although the condition also occurred to a large extent on the arms, chest and back and to a lesser degree on the legs.

The general appearance of the patient was good. She had not been losing weight; no history was given of any symptoms which might suggest other causes for the eruption, and there had been no previous or preexisting eruptions. The Wassermann reaction of the blood on admission was negative, and urinalysis and chemical analysis of the blood gave negative results. The blood pressure was 124 systolic and 74 diastolic. Analysis of the urine for arsenic showed the following values: October 3, with a volume of 1,150 cc. of urine, the arsenic, as arsenic trioxide, amounted to 10 mg. per hundred cubic centimeters (total, 115 mg.); December 4, with a volume of 1,310 cc. of urine, the arsenic amounted to 0.05 mg. per hundred cubic centimeters (total, 0.65 mg.).

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1. Epstein, E.: Sensitivity to Both Trivalent and Pentavalent Arsenicals, Arch. Dermat. & Syph. **36**:964 (Nov.) 1937.

2. Golz, H. H.: Sensitivity to Arsenical Drugs, Am. J. Syph., Gonor. & Ven. Dis. **23**:344, 1939.

Physical, fluoroscopic, roentgenographic and cardiac examinations gave negative results. The electrocardiogram showed left axis tendency within normal range. The physical examination showed no abnormalities except that the right pupil was larger than the left. Both eyes reacted to light and in accommodation, the right being somewhat more sluggish; the media were clear and the fundi normal.

The patient was hospitalized shortly after she entered the clinic. She was then treated by baths and local application of a calamine emulsion and later of salicylated oil. The diet was restricted, and the regimen was followed which is usual in the care of a patient with exfoliative dermatitis. Superficial roentgen therapy was used, with apparent good effect. After several weeks, the patient was returned to the clinic. She received five injections of sodium thiosulfate and twenty-four injections of liver extract, intramuscularly. A cisternal puncture was performed March 27, 1940, about six months after initial treatment at this clinic. The findings were as follows: The Wassermann reaction in plain beef heart was plus-minus in 0.2 cc. and 3 plus in 0.3 cc.; in cholesterolized beef heart, 1 plus in 0.2 cc. and 4 plus in 0.3 cc.; the colloidal gold curve was 00111100000; white cells per cubic millimeter amounted to 6, and the butyric acid test gave a negative reaction.

On April 5 the patient was given an intravenous injection of 0.5 Gm. of tryparsamide. Two days later she noticed a generalized burning and itching, especially of the face. This was followed by a macular eruption which soon involved most of the body. There were severe erythema and edema, followed by some vesiculation.

Antisyphilitic therapy was stopped, and supportive treatment was reinstituted. In about three weeks the patient had improved sufficiently so that it was deemed safe to administer artificial fever therapy.

Case 2.—Mrs. E. B., aged 43, born in Germany and a resident in this country for two years, was admitted to the board of health clinic at Paterson, N. J., to resume treatment for syphilis.

She gave the following history: She had never been ill until she was 26 years old, when suddenly she had chills, fever and severe pains in all her joints. The Wassermann reaction of the blood was positive. Antisyphilitic treatment was instituted. After the third injection of arsphenamine, she became violently ill and again had chills, fever and a rash, which necessitated her being confined to a hospital for several weeks. Wassermann reactions on discharge from the hospital and once every six months until 1938 were negative.

When she was 37 years of age, a tonsillectomy was performed under local procaine anesthesia, after which she became ill with chills, fever and a rash. She remained in the hospital for six weeks.

In 1938, when the patient was 41, she came to this country. She came to the clinic for examination and to continue treatment for syphilis. The general appearance of the patient was good. A Wassermann reaction of the blood on admission was 4 plus. The blood pressure was 130 systolic and 76 diastolic. The urine was normal. A Romberg test gave a positive result. The pupils reacted to light and in accommodation; the right pupil was slightly irregular, and the visual fields and the optic nerves were normal. The patellar reflexes were both absent. Examination of the spinal fluid showed 5 white cells per cubic millimeter, a 4 plus Wassermann reaction with plain beef heart in 0.2 cc., no globulin and a colloidal gold curve of 5543210000.

Beginning in January 1939 and ending October 1, the patient was given forty-one injections of a bismuth compound and iodides by mouth. On October

6 she was given 0.3 Gm. of tryparsamide as a test dose. In about three hours she became chilly and the skin over the entire body became erythematous and edematous. The following day there was generalized pruritus, especially of the face and neck. There was a generalized edematous erythematous macular eruption, which was followed by mild vesiculation and exfoliation.

All antisyphilitic therapy was discontinued and general supportive treatment was instituted. The usual treatment for exfoliative dermatitis was given, including sodium thiosulfate intravenously.

In about six weeks the skin gradually returned to its normal appearance.

COMMENT

It is generally known that once a severe reaction from an arsenical compound occurs, caution must be used in again giving the patient the same preparation or related drugs. Yet it has not been generally recognized that reaction caused by a trivalent arsenical compound may produce sensitization to a pentavalent arsenical compound. One is led to believe from the literature that pentavalent arsenic causes little reaction except in the eye. Isolated instances of reaction caused by tryparsamide have been reported by Skoog,[3] O'Leary and Becker,[4] Robinson,[5] Astrachan and Franks [6] and many others.

SUMMARY

Two cases of arsenical dermatitis following neoarsphenamine therapy are reported. Recurrence of the dermatitis took place on the institution of tryparsamide therapy.

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3. Skoog, L.: Tryparsamide Therapy in Neurosyphilis, J. Missouri M. A. **22**:387, 1925.

4. O'Leary, P., and Becker, S.: Further Observation on the Treatment of Neurosyphilis with Tryparsamide, M. J. & Rec. **12**:305, 1936.

5. Robinson, S. S.: Tryparsamide Dermatitis, Arch. Dermat. & Syph. **34**:251 (Aug.) 1936.

6. Astrachan, G. D., and Franks, A. G.: Nitritoid Reaction Following an Injection of Tryparsamide, Arch. Dermat. & Syph. **38**:949 (Dec.) 1938.

"BUBONULUS" IN LYMPHOGRANULOMA VENEREUM

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The term "bubonulus" (small bubo) is used to designate a bubo-like swelling that may occur in chancroid at sites other than the groin, particularly on the penis. The swelling is smaller than a regular bubo and, moreover, is not a bubo at all. There is no invasion of the lymph glands, but there is a circumscribed infiltration around lymph vessels.

Infiltrations in the lymph vessels imitating the typical lymphadenitis more or less closely can be encountered in such diseases as tuberculosis [1] and tularemia. In lymphogranuloma venereum such an occurrence does not seem to have attracted attention, although the importance of the involvement of the lymph vessels is well recognized for this disease.

I saw 3 patients in whom a bubonulus developed after infection with lymphogranuloma venereum.

REPORT OF CASES

CASE 1.—W. E., a Negro aged 28, three years before the appearance of the present disease observed a chancroidal bubo (typical clinical appearance, positive reaction to the cutaneous test for chancroid, negative reaction to the Frei test and positive culture of Ducrey's bacillus from aspirated pus). The lesions healed without further treatment. On Jan. 27, 1939 the patient presented himself again, complaining of a penile lesion of three weeks' duration and of swelling in both groins. The ulcer of the penis, 10 mm. in diameter, was situated in the dorsal part of the coronary sulcus, as well as in the adjacent area of the glans, and was depressed in the center and shallow in the periphery. The buboes were fluctuant, not tender and not acutely inflamed. In addition to the positive result of the test for chancroid, the Frei test also gave a positive result at this time (2 plus increasing to 3 plus). Pus was aspirated from the buboes, and it supplied an excellent Frei antigen, giving strong, specific reactions in patients who had been proved to have lymphogranuloma venereum. The patient then vanished from observation. On April 11 he came back because of swelling of the penis. In the meantime he had received some antisyphilitic treatment. Examination revealed a circumscribed elevation at the right lateroinferior aspect of the prepuce, which was soft, fluctuant and 1 by 1.5 cm. in size. There was little tenderness and no acute inflammation. Collateral

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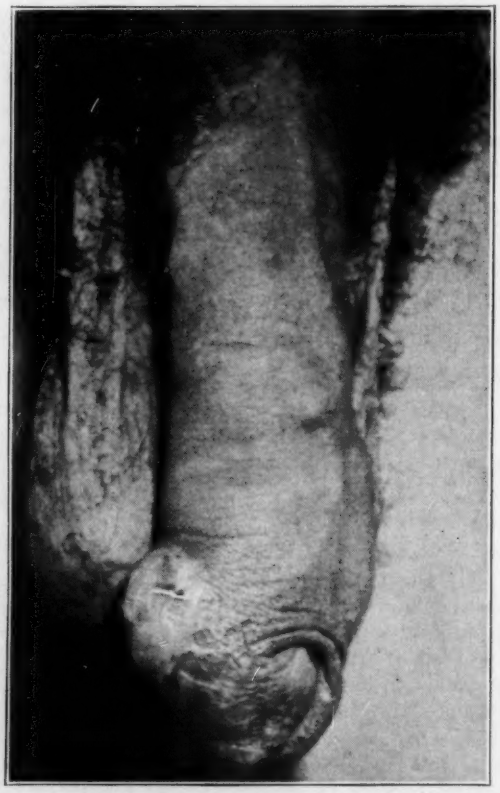
This investigation was aided by a grant from the United States Public Health Service.

1. Metcalf, W. B.: Tuberculosis of the Lymphatic System, New York, The Macmillan Company, 1919, p. 104. Kaufmann, E.: Pathology, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 1, p. 175.

edema was present (see figure). The glands in the right groin were slightly swollen, and those in the left groin were moderately swollen, firm and discrete. A few scars indicated previous suppuration. Chancroid and Frei tests gave 4 plus reactions. Suppuration of the penile lesion was progressive, and on April 18 greenish yellow pus in the unexpected amount of 5 cc. was aspirated. Bacillus Ducrey could not be demonstrated by culture. On the other hand, a specific Frei antigen could be prepared from the pus. Other points to define the nature of the bubonulus were: the development during an infection with lymphogranuloma



Bubonulus in a patient with lymphogranuloma venereum, with edema of prepuce and phimosis.

venereum; the considerable time that had elapsed since the previous infection with chancroid; the clinical appearance of the lesion in question (only slight tenderness and absence of acute inflammation), and the continuous increase in the strength of the Frei reaction (negative, 2 plus, 3 plus and 4 plus).

CASE 2.—P. L., a Negro aged 57, came to the clinic on March 28, 1939 and presented typical chancroidal ulcer, 8 by 10 mm. in diameter, on the glans penis. The inguinal glands were slightly swollen. The test for chancroid gave an exceedingly strong reaction, with subsequent development of a vesicle. The Frei test

gave a slight reaction. The Wassermann reaction had been 4 plus for a year, but the patient had not undergone treatment. Sulfanilamide treatment was instituted. The patient did not return until Feb. 19, 1940. He reported that the sores had quickly disappeared but that new ones had appeared a few days previously. In the coronary sulcus two ulcers could be seen, the appearance of which did not exclude chancroid (deep and partly undermined). The Frei test, however, gave a 4 plus result at this time, and the inguinal glands were enlarged, fused and not tender. Sulfanilamide was given in daily doses, decreasing from 80 to 40 grains (5 to 2.5 Gm.). On February 26 the ulcers were diminished in size. An eminence developed on the dorsal aspect of the penis, in the area of the sulcus coronarius, which was best seen with the prepuce in normal position. On retraction of the foreskin, the eminence was better felt than seen. It was firm, elastic, not tender and not acutely inflamed. It extended to the subcutis and was well defined, except at the inferior part, where it merged with the margin of the glans penis just behind and beneath one of the ulcers. On March 7 the ulcers were healing, the bubonulus was harder and smaller, and a cordlike connection to the nearby ulcer could be palpated. On March 19, after complete epidermization, the administration of sulfanilamide was discontinued and antisyphilitic treatment was instituted. On May 21 during treatment with neoarsphenamine new ulcerations developed. The bubonulus was still present. The direct evidence, by using pus from the bubo (and bubonulus) for a Frei antigen, was not feasible in this case. Nevertheless, the diagnosis seemed certain. Evidently the first lesions were chancroid. As for the second lesions (February 1940), the 4 plus Frei reaction and the qualities of the buboes as well as of the bubonulus suggested lymphograuloma venereum. Gumma was almost ruled out by the recurrence of the ulcers during antisyphilitic treatment.

CASE 3.—W. T., a Negro aged 25, on May 12, 1939 presented a bubo of six days' duration in the right groin. The bubo was the size of an egg and was fluctuant. Aspiration yielded 2 cc. of pus which supplied an excellent Frei antigen. The glands in the left groin were enlarged. On the inner side of the prepuce was a round, well defined superficial ulcer, 5 mm. in diameter, soft, not tender and covered with purulent discharge. The test for chancroid gave a negative reaction, and the Frei test gave a 4 plus result. On May 22 behind the ulcer a prominent infiltration had developed, 5 by 12 mm. in size, firm with softening in the center, not tender and not acutely inflamed. Sulfanilamide was administered. On May 26 a new area of suppuration appeared in the buboes. The bubonulus was regressing. On July 5 all the lesions were healed.

The direct evidence from the pus, the qualities of the ulcer, buboes and bubonulus, the result of the cutaneous tests and the absence of a previous chancroid infection prove unanimously that the lesion in question was part of lymphogranuloma venereum.

SUMMARY

Three cases of lymphogranuloma venereum are reported, in each of which a circumscribed bubo-like eminence developed on the penis. The lesions were much smaller than a true bubo and, moreover, were not related to lymph glands. The term "bubonulus," as used for circumscribed infiltration around lymph vessels in chancroid, seems to be proper for this lesion of lymphogranuloma venereum also.

ARSPHENAMINE ENCEPHALOPATHY

REPORT OF UNUSUAL CLINICAL AND HISTOLOGIC OBSERVATIONS

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The clinical and pathologic observations in cases of hemorrhagic encephalopathy due to arsphenamine usually present a fairly characteristic picture. A few hours or days after an intravenous injection of an arsphenamine preparation acute cerebral symptoms develop, especially headache, nausea, vomiting and fever, and the patient rapidly becomes comatose. Meningitic signs are usually absent except in cases in which subarachnoid bleeding has occurred. The cerebrospinal fluid is usually normal except for having increased pressure. Autopsy generally reveals marked dilatation and engorgement of the meningeal and cerebral vessels, varying degrees of vascular necrosis and perivascular hemorrhages, typically of the "ring" type. Meningeal hemorrhages may be present. A mild perivascular inflammatory infiltration is sometimes noted. Perivascular softening and demyelinization as the outstanding lesion has been described.[1]

The case herein reported is unusual in that it presented a frank meningitic as well as encephalopathic syndrome and because of the unusually intense leukocytic inflammatory reaction in the brain substance.

REPORT OF A CASE

A 19 year old white youth was admitted in coma to the neuropsychiatric service of Dr. Roy R. Grinker at the Michael Reese Hospital on Oct. 28, 1939.

History.—About two months previously cutaneous manifestations of secondary syphilis had developed, especially condylomata lata. The patient was treated at the Municipal Contagious Disease Hospital with two injections of a bismuth preparation and four intravenous injections of neoarsphenamine, the first consisting of 0.3 Gm. and the subsequent three injections of 0.45 Gm. each. The last injection was given three days before admission to Michael Reese Hospital, and the patient was discharged from the Municipal Contagious Disease Hospital apparently well. The following day he complained of headaches, vomited several times and had a temperature of 102 F. On the morning of admission he began to feel better but suddenly went into coma in the afternoon.

From the Department of Neuropsychiatry of the Michael Reese Hospital.

1. Russell, D. S.: Changes in the Central Nervous System Following Arsphenamine Medication, J. Path. & Bact. **45**:357, 1937.

Examination.—On admission that evening the patient was deeply comatose and in extremis. The temperature was 103.8 F.; the pulse rate was 110, and the respirations were stertorous. There was decided diaphoresis. The blood pressure was 116 systolic and 72 diastolic. The ears, nose and throat were normal. Chest expansion was good, equal on the two sides. Coarse, bubbling rales were heard all over the chest, obscuring the breath sounds. The heart was of normal size and configuration, with normal sounds, and no adventitious sounds were heard. The abdominal muscles were rather rigid, and no viscera were palpable. The patient lay in a position resembling that of decerebrate rigidity, with the legs rigidly extended. Frequent involuntary random movements and fluctuations in the tonus of the upper extremities were noted. The neck was moderately stiff. The pupils were small and irregular and reacted only slightly to light. No abnormalities were observed in the fundi. There was left internal strabismus. The reflexes in the upper extremities were hyperactive; those of the lower extremities could not be obtained. The Babinski sign was present on both sides, more evident on the right.

The original clinical impression included several diagnostic possibilities. The most likely was acute syphilitic meningitis with encephalitic involvement or acute hemorrhagic encephalopathy with meningeal hemorrhage due to arsphenamine intoxication.

Diagnostic lumbar puncture revealed turbid spinal fluid under a pressure of 210 mm. of water. The cell count was 1,200 per cubic millimeter, 80 per cent of which were polymorphonuclear leukocytes, and no red cells were noted. The Pandy test gave a 4 plus reaction. An emergency Wassermann test of the spinal fluid gave a 4 plus reaction, and the Lange curve was 0000035555. Qualitative tests revealed no sugar. The smear was negative for organisms, and a culture revealed no growth after forty-eight hours.

In view of the meningitic syndrome with a polymorphonuclear pleocytosis and a positive Wassermann reaction of the cerebrospinal fluid, a diagnosis of acute syphilitic meningoencephalitis was made, and treatment with large doses of intravenous iodides was begun. The patient, however, failed to rally from his moribund state; a rapidly increasing hyperpyrexia developed, with a temperature of 108 F., and he died during the same night.

General Pathologic Examination.—Necropsy was performed by Dr. Otto Saphir, of the laboratory of pathology of the Michael Reese Hospital, who gave me the following description of the general pathologic changes.

There was generalized lymphadenopathy, including the epitrochlear glands. A pigmented scar was present on the right side of the shaft of the penis. The mesenteric lumbar and iliac lymph nodes were enlarged.

Small pinpoint hemorrhages were seen in the pericardium and endocardium, with a hemorrhagic area several millimeters in diameter in the wall of the left ventricle. Microscopic sections through the lesions showed them to consist of collections of red blood cells surrounding necrotic arterioles, recognizable only as pale pink, granular, ring-shaped structures. Numerous polymorphonuclear leukocytes were clustered about the necrotic vessels. In many places the muscle fibers were separated by collections of red blood cells. Focal necroses of the myocardial coronary vessels were present.

Grossly the pleural surfaces of the lungs were flecked with small and large hemorrhages. The cut surface of the right lung revealed numerous dark red, firm elevated areas. Microscopically the bronchioles were filled with polymorphonuclear leukocytes. In sections of the lower lobe, the alveoli surrounding each

bronchiole were distended with polymorphonuclear leukocytes, red blood cells, eosinophilic precipitate and pigment-laden endothelial leukocytes. Other sections revealed engorged alveolar blood vessels and collections of red blood cells in the alveoli.

Grossly and microscopically the liver showed vascular engorgement. The hepatic cells showed toxic changes, consisting of vacuolation, granules, basophilic staining and loss of nuclei.

The spleen was enlarged and of unusually soft consistency. Microscopically the splenic pulp was intensely hemorrhagic, with large collections of extrasinusoidal red blood cells.

The kidneys contained no hemorrhages, but there was engorgement of the blood vessels. Many cells of the convoluted tubules were granular and had indistinct outlines.

Gross linear hemorrhages were present in the small intestine. The lymph follicles in the ileocecal region and in the rectum were prominent and contained numerous pinpoint hemorrhages. Microscopically the mucosa contained numerous perivascular extravasations of red blood cells.

The pancreas contained engorged blood vessels.

The general pathologic diagnosis was multiple hemorrhages of the pericardium, myocardium, endocardium, pleura, diaphragm and small and large intestines; focal toxic degeneration of the liver; bronchitis, bronchiolitis and bronchopneumonia; acute splenic hyperplasia, and generalized lymphadenopathy with lymphoid hyperplasia of the intestine.

Pathologic Examination of the Brain.—When the calvarium was removed, the brain was seen to be swollen and the convolutions to be flattened. The meningeal vessels were decidedly injected. After fixation in solution of formaldehyde the following gross abnormalities were noted. The leptomeninges appeared thickened, especially over the frontal convexities near the midline. The pial vessels over the cortex were distended with blood, and the brain appeared swollen. On gross examination no blood was found in the subarachnoid space. The most striking feature of the cut surfaces of the brain were the hemorrhages distributed throughout the entire brain. The regions involved were the basal ganglia, the pons and the medulla most severely, the deep subcortical white matter to a lesser extent and the gray cortex the least. Many hemorrhages were present in the central nuclear portion of the cerebellum. These hemorrhages were for the most part small and discrete, pinpoint in size. In the severely involved areas of the brain stem, however, the small hemorrhagic foci were so close together that in places they appeared confluent.

Microscopic sections from various parts of the brain revealed the following changes: The meninges were irregularly thickened and infiltrated with an inflammatory exudate and small numbers of red blood cells (fig. 1). The collections of inflammatory cells varied a great deal in density, being only a few cells in thickness in some places but in others reaching dense massive proportions. The collections consisted of large and small lymphocytes, plasma cells and large numbers of polymorphonuclear leukocytes. There were an increase in the number of blood vessels and many dilated vessels. Extravasated red blood cells were found lying free among the inflammatory cells in many places, but the vessel walls were intact and did not present the necrotic changes noted in the vessels within the brain substance.

A section through various parts of the cortex, basal ganglions and brain stem revealed pathologic changes involving most conspicuously the blood vessels and

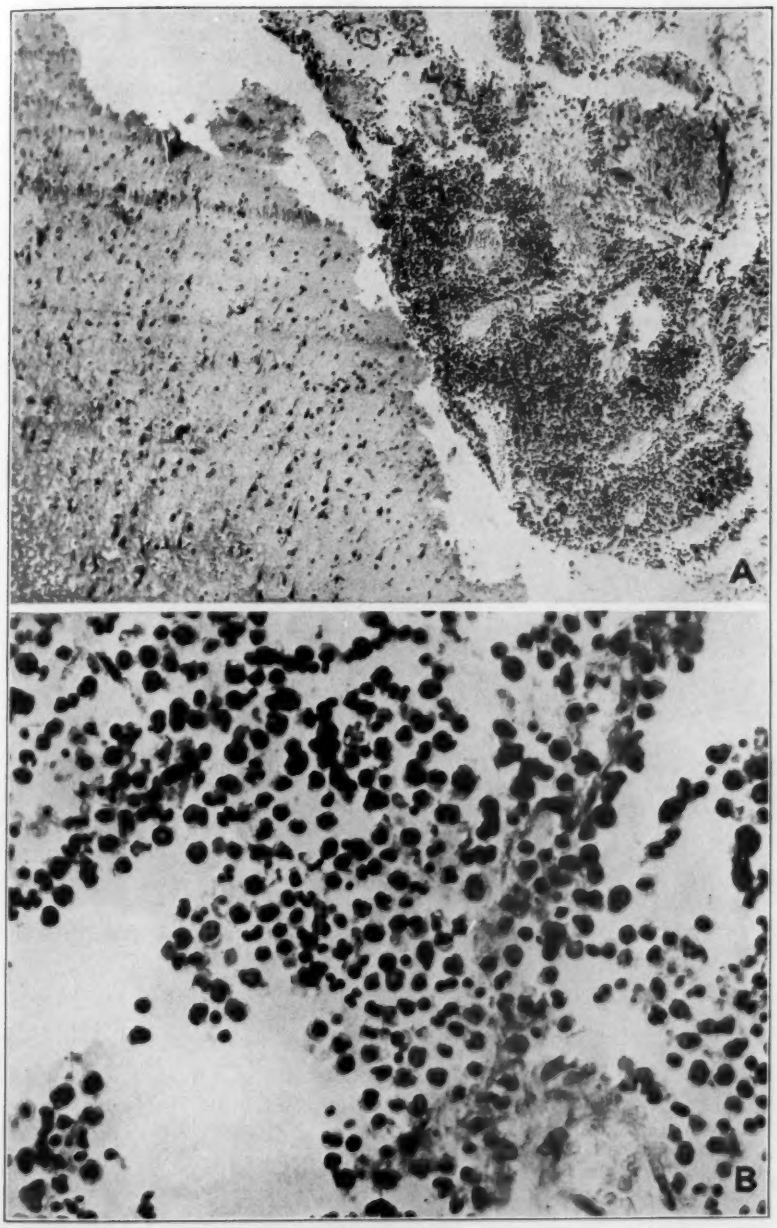

Fig. 1.—Meningeal exudate. *A*, section under low power (hematoxylin and eosin stain; × 68). *B*, high power, showing polymorphonuclear leukocytes, lymphocytes and plasma cells (hematoxylin and eosin; × 420).

the perivascular regions. The vessels were everywhere dilated and engorged and contained large numbers of leukocytes. The vessel walls, especially of venules and arterioles, were frequently necrotic, either focally or in their entirety, many being converted into structureless rings (fig. 2). These necrotic walls were infiltrated with lymphocytes and polymorphonuclear leukocytes, many of which were themselves pyknotic. In these areas the capillaries stood out conspicuously because of the intense perivascular lymphocytic and leukocytic infiltration (fig. 3). In the most severely involved portions these inflammatory cells were found to have infiltrated the surrounding tissue of the brain a considerable distance from the blood vessels. Perivascular hemorrhages were numerous, but none of the typical "ring" type were observed. In many places the extravasations of blood extended

Fig. 2.—Necrotic vessel walls in brain (hematoxylin and eosin; × 320).

far into the adjacent parenchyma. Throughout the involved regions were numerous inflammatory foci about the vessels, the walls of which in many instances were necrotic but without any extravasation of red cells.

The foci of vascular necrosis, inflammatory infiltration and hemorrhage were found for the most part in the deep white matter and in the brain stem but were also present in small numbers in the gray cortex. Edema of the cortex and the white matter was everywhere. No foci of perivascular demyelination were found except in the foci of perivascular hemorrhagic or inflammatory infiltration.

The only glial reaction was a slight increase in oligodendroglia cells throughout the affected white matter.

A search for spirochetes by means of the Levaditi stain gave negative results, and no micro-organisms could be found with bacterial stains in the brain substance or in the meninges.

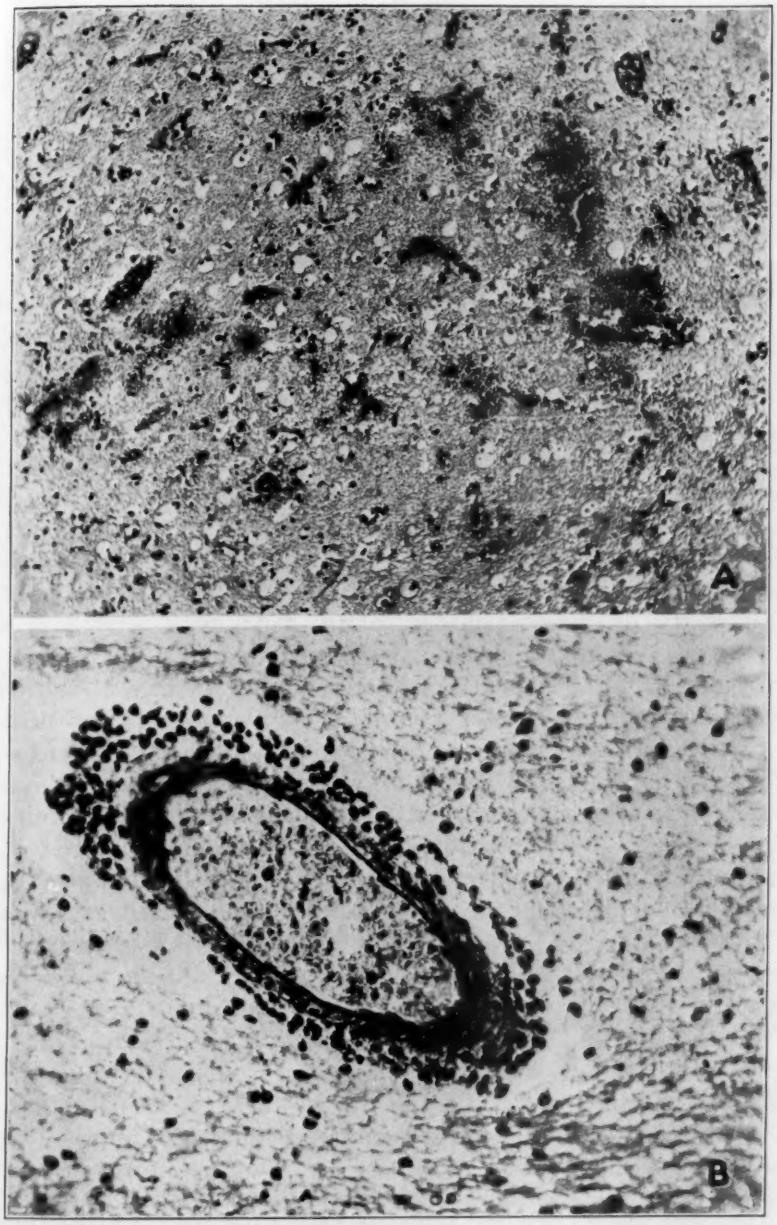

Fig. 3.—Brain stem. *A*, vessels surrounded by inflammatory cells; numerous small discrete hemorrhages (hematoxylin and eosin; × 320). *B*, perivascular infiltration with leukocytes and lymphocytes (hematoxylin and eosin; × 200).

COMMENT

The first point of interest in this case is the question of the clinical diagnosis. In view of the history of recent secondary syphilis, the meningitic syndrome with pleocytosis (1,200 lymphocytes, with 80 per cent polymorphonuclear leukocytes) and a 4 plus Wassermann reaction of the cerebrospinal fluid, the diagnosis of acute syphilitic meningitis was made in preference to one of arsphenamine hemorrhagic encephalopathy. When meningitic signs are present in the latter condition, they are usually due to subarachnoid hemorrhage, the cerebrospinal fluid evidence of which was absent in this case.

A survey of the literature reveals that pleocytosis is usually not present. "Meningitic" signs and findings of "meningitis" pathologically in cases taken from the literature are reported by Glaser, Imerman and Imerman,[2] but no description of the cerebrospinal fluid or of the histologic picture is given.

On gross examination of the brain the numerous small hemorrhages immediately pointed to hemorrhagic encephalopathy due to arsphenamine, possibly complicating syphilitic meningitis. The histologic observations, however, were unlike those of syphilis of the brain, as they consisted of a decided polymorphonuclear as well as lymphocytic infiltration, widely disseminated throughout the parenchyma as well as the meninges. A mixed polymorphonuclear and lymphocytic exudate is seen in acute syphilitic meningitis, but the encephalitic exudate is limited to the perivascular zones. The necrosis of the vessel walls was characteristic of the toxic necrosis seen in typical cases of arsphenamine poisoning, as were the changes in the vascular apparatus and the hemorrhages in many of the viscera. Although the failure to find spirochetes does not in itself conclusively exclude the possibility of syphilis, it is suggestive. The 4 plus Wassermann reaction of the cerebrospinal fluid was evidently due to the presence of blood in the perivascular and subarachnoid spaces. It seems reasonable, therefore, to ascribe the vascular lesions, the hemorrhagic and inflammatory changes in the parenchyma and the meningitic reaction to the toxic effect of the arsphenamine. Such an intense and conspicuous inflammatory reaction must be extremely unusual, as mild leukocytic and lymphocytic perivascular infiltrations have been noted by only a few writers,[1] including Black,[3] in whose case the perivascular inflammatory infiltration was most probably due to meningovascular syphilis.

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2. Glaser, M. A.; Imerman, C. P., and Imerman, S. W.: So-Called Hemorrhagic Encephalitis and Myelitis Secondary to Intravenous Arsphenamins, Based on Review of One Hundred and Fifty-Eight Cases, Am. J. M. Sc. **189**:64, 1935.

3. Black, W. C.: Death from Hemorrhagic Encephalitis Following Treatment with Sulpharsphenamine: Report of Two Cases in Syphilitic Infants, Am. J. Dis. Child. **51**:609 (March) 1936.

SUMMARY

A clinicopathologic report of a case of hemorrhagic encephalopathy due to arsphenamine is reported. The unusual features of a severe meningeal inflammatory reaction and an intense leukocytic and lymphocytic infiltration of the vessel walls and parenchyma of the brain are described, in addition to the usual vascular necroses and perivascular hemorrhages.

30 North Michigan Avenue.

EPITHELIOMA ADENOIDES CYSTICUM, TRICHOEPITHELIOMA AND BASAL CELL CANCER

RELATION BETWEEN THESE DISEASES, AS SHOWN BY HISTOLOGIC STUDIES OF MULTIPLE BENIGN CYSTIC EPITHELIOMA

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BUFFALO

A genetic relation between epithelioma adenoides cysticum (Brooke), trichoepithelioma and some examples of basal cell cancer has long been suspected. However, the concept that these conditions have a common embryonic origin has received little more than passing comment in the American literature during the past two decades. In short, effort in this field has been directed rather to the establishment of somewhat rigid clinical entities than toward an understanding of pathologic circumstances which might be common to all of them—or, at least, of which they were more or less a considerable part.

Still, certain earlier writers took the broader view of the subject. Indeed, the idea of a possible relation between epithelioma adenoides cysticum and perverted development of hair follicles is as old as the classic description of the disease. Brooke,[1] in histologic sections from 2 of his cases, noted that the masses of basal cells in the corium appeared to originate both in the basal cell layer of the epidermis and in the epithelium of hair follicles. Moreover, the cystic spaces formed by these masses of cells contained concentric layers of horny material and occasionally a hair shaft. Fordyce[2] made the same observation almost simultaneously.

From the Laboratory of Dermatological Research, University of Pennsylvania.

Read before the Section on Dermatology at the Ninety-First Annual Session of the American Medical Association, New York, June 14, 1940.

This work was made possible by the fact that the following physicians loaned me histologic material: In the cases in group I were those of 7 members of one family, which Dr. Hyman Goldman is reporting in another paper; other contributors were Drs. John V. Ambler, Denver; Carey C. Barett, Lexington, Ky.; Samuel Feldman, New York; William H. Guy, Pittsburgh; L. W. Ketron, Baltimore; C. F. Lehman, San Antonio, Texas; A. J. Markley, Denver; Hamilton Montgomery, Rochester, Minn.; O. S. Philpott, Denver; Raymond V. Quinlan, Meriden, Conn.; Braulio Saenz, Habana, Cuba; A. W. Stillians, Chicago; Richard L. Sutton Jr., Kansas City, Mo., and L. H. Winer, Minneapolis.

1. Brooke, H. G.: Epithelioma Adenoides Cysticum, Brit. J. Dermat. **4**:269 (Sept.) 1892.

2. Fordyce, J. A.: Multiple Benign Cystic Epithelioma, J. Cutan. Dis. **10**:459 (Dec.) 1892.

Jarisch [3] went further, stating that the masses of cells originated chiefly in the sheaths of hair follicles, and therefore suggested the name trichoepithelioma papulosum multiplex. Hartzell,[4] too, held that the cellular masses of the Brooke tumor were overgrown and distorted hair follicles. He favored the term trichoepithelioma to the exclusion of all others. McDonagh [5] reported combined trichoepithelioma papulosum and syringocystadenoma in a single sample of tissue, in which the hair follicle element resembled the cellular masses in Brooke's cases but the cells were more mature; they evidently had the potentiality for further differentiation and, accordingly, had succeeded in forming lanugo hair follicles with embryonic sebaceous glands. He interpreted these findings as indicating that the cells forming the rudimentary hair follicle were "cut off" later in embryonic life than those in Brooke's cases. Adamson [6] and Little,[7] as well as Paul and Inglis,[8] were also in accord with the idea that in epithelioma adenoides cysticum the tumors resulted from attempts on the part of embryonic cells to form hair follicles.

Savatard [9] stated that some of the cystic masses formed structures that appeared to be rudimentary sebaceous glands, which further identified the process with the development of a pilosebaceous structure. However, neither his illustrations nor his text indicate that sebaceous cells were active participants in the hyperplastic processes. He maintained further that the pigment so commonly seen in the cysts was elaborated by the surrounding epithelial cells and was a part of this picture of attempted hair follicle formation. In his opinion, the tumors belong to a large group of nevi; that is, they are of embryonic origin and might well be called follicular nevi of the skin.

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3. Jarisch: Zur Lehre von den Hautgeschwülsten, Arch. f. Dermat. u. Syph. **28**:163, 1894.

4. Hartzell, M. B.: Benign Cystic Epithelioma, Brit. J. Dermat. **16**:361, 1904.

5. McDonagh, J. E. R.: Case of a Mixed Tumor (Trichoepithelioma Papulosum and Syringocystadenoma), Proc. Roy. Soc. Med. (Sect. Dermat.) **3**:32 (Dec.) 1910.

6. Adamson, H. G.: On the Nature of Rodent Ulcer: Its Relation to Epithelioma Adenoides Cysticum of Brooke and to Other Trichoepitheliomata of Benign Nevoid Character; Its Distinction from Malignant Carcinoma, Lancet **1**: 810 (March 21) 1914.

7. Little, E. G.: A Note on Two Cases of Epithelioma Adenoides Cysticum (Brooke), Trichoepithelioma Papulosum Rodens (Jarisch), Brit. J. Dermat. **26**: 173, 1914.

8. Paul, N., and Inglis, K.: Case of Epithelioma Adenoides Cysticum (Brooke), Brit. J. Dermat. **39**:195 (May) 1927.

9. Savatard, L.: Epithelioma Adenoides Cysticum, Brit. J. Dermat. **34**:381 (Dec.) 1922.

Kyrle [10] also stated the belief that the tumors of multiple benign cystic epithelioma were hair follicle nevi, which histologically could show great variations in degree of maturity. He regarded them as "heterologous hamartoma."

In a patient with adenoma of the sweat glands of the shoulder and epithelioma adenoides cysticum on the face, Weidman and Besancon [11] observed in the microscopic sections of the facial lesions that hair follicles were present in various stages of development.

Whereas there is thus a large unanimity in the foregoing, when the relations of basal cell cancer to this field are considered, one finds considerable difference of opinion, and it is in this connection that our materials and studies have the larger bearing and import. Jarisch [3] proposed the name trichoepithelioma papulosum multiplex rodens for those conditions resembling multiple rodent ulcer. Clinical similarity between the two conditions was also observed by White,[12] who in 1894 reported a case of multiple benign cystic epithelioma in which some of the lesions that had ulcerated appeared exactly like those in rodent ulcer. He questioned whether the disease could be considered benign. Later, Hartzell [13] also questioned the benign character of the disease and commented on the increasing number of reported cases in which ulceration had occurred. Sutton and Dennie,[14] Little,[7] Miller,[15] Schamberg [16] and others have also reported such cases. In this connection, Summerill and Hutton [17] in their complete review of the literature adhered to the concept of a strictly distinct clinical syndrome. Incidentally, and singularly, they eliminated from that category all the reported cases in which ulceration had occurred; these they considered

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10. Kyrle, J.: Epithelioma adenoides cysticum, in Vorlesungen über Histo-Biologie der menschlichen Haut und ihrer Erkrankungen, Berlin, Julius Springer, 1925, vol. 1, p. 239.

11. Weidman, F. D., and Besancon, J. H.: Histologic Differences in "Syringoma" of Face and Shoulder: Employment of Wax Reconstruction, Arch. Dermat. & Syph. **21**:279 (Feb.) 1930.

12. White, J. C.: Multiple Benign Cystic Epithelioma, J. Cutan. Dis. **12**:477, 1894.

13. Hartzell, M. B.: A Further Contribution to the Study of Benign Cystic Epithelioma, J. M. Research **18**:159, 1908.

14. Sutton, R. L., and Dennie, C. C.: Possible Interrelationship of Acanthoma Adenoides Cysticum (Multiple Benign Cystic Epithelioma) and Syringocystadenoma (Lymphangioma Tuberosum Multiplex), J. A. M. A. **58**:333 (Feb. 3) 1912.

15. Miller, J. W.: Multiple Benign Cystic Epithelioma, J. Cutan. Dis. **33**:462 (June) 1915.

16. Schamberg, J. F.: Multiple Benign Cystic Epithelioma, J. Cutan. Dis. **27**: 170, 1909.

17. Summerill, F., and Hutton, J. G.: Multiple Benign Cystic Epithelioma (Epithelioma Adenoides Cysticum), with Summary of Literature, Arch. Dermat. & Syph. **26**:854 (Nov.) 1932.

to be basal cell epithelioma of the Krompecher type. It is doubtful, however, whether ulceration should be depended on as a sole criterion of malignancy in any lesion.

McDonagh [18] disputed the thesis that epithelioma adenoides cysticum, trichoepithelioma and rodent ulcer were separate clinical and histologic entities. He stressed the point that great variations are seen in each; in a case of typical clinical epithelioma adenoides cysticum the condition could histologically resemble a more mature trichoepithelioma or could be so embryonic as to be microscopically indistinguishable from rodent ulcer. These variations he interpreted as being "links in one pathological chain," dependent on the time the cells forming the tumor were laid down in embryonic life.

Adamson [6] agreed with these views and stated that both multiple benign cystic epithelioma and rodent ulcer are variations of trichoepithelioma and are nevoid growths in the sense of Cohnheim's theory. In addition, he called attention to the distribution of the lesions of multiple benign cystic epithelioma on the face. This corresponded almost exactly with the location of the lesions in 220 cases of rodent ulcer analyzed by Sequeira. More recently, McFarland, Ciconne and Gelehrter [19] have similarly concluded that basal cell cancers originate in imperfections in the closure of the embryonal facial fissures.

While the question does not belong strictly within the scope of this work, it is unavoidable after this to consider whether all basal cell cancers are related to the hair follicle. Suffice it say that both Mallory [20] and Haythorn [21] supported such an idea (i. e., all basal cell cancers are "hair matrix carcinomas"). On the other side, Montgomery [22] favored Krompecher's original theory of the basal cell origin of these tumors and agreed with Kyrle that a distinction must be made between benign and malignant forms of basal cell epithelioma. The former, he stated, may in some cases originate in the hair follicles, whereas the latter seldom do.

Boyd [23] properly suggested that all basal cell cancers need not necessarily originate in the same way; he cited the basal layer of the epi-

18. McDonagh, J. E. R.: Pathology of Skin from the Eyelids and Nasofacial Grooves, Brit. J. Dermat. **24**:291, 1912.

19. McFarland, J.; Ciconne, E. F., and Gelehrter, J.: On Dysontogenetic Origin of Basal Cell Carcinoma, Am. J. Cancer **25**:273 (Oct.) 1935.

20. Mallory, F. B.: Recent Progress in the Microscopic Anatomy and Differentiation of Cancer, J. A. M. A. **55**:1513 (Oct. 29) 1910.

21. Haythorn, S. R.: Studies on Histogenesis of So-Called "Basal Cell Carcinoma," Am. J. Cancer **15**:1969 (July) 1931.

22. Montgomery, H.: Histogenesis of Basal Cell Epithelioma, Radiology **25**: 8 (July) 1935.

23. Boyd, W.: The Pathology of Internal Diseases, ed. 2, Philadelphia, Lea & Febiger, 1935, p. 325.

dermis, the hair follicles and misplaced cell groups from the epidermis as possible sites of origin. Stout [24] expressed a similar opinion.

There is thus a large accumulation of literature bearing scatteringly on the relation of epithelioma adenoides cysticum to trichoepithelioma on the one hand and to rodent ulcer on the other. It has occurred to me that a series of relations might be constructed if the entire situation were studied and analyzed from the standpoint of the embryologic development of the hair follicle. Accordingly, in studying my series of cases the various steps in the embryologic development of the skin have been visualized, and the attempt has been made to reconcile them with the features observed in the histologic sections.

SCOPE AND LIMITATION OF TRICHOEPITHELIOMA

At this point it is proper to indicate the sense in which the term trichoepithelioma is employed in this paper. First and foremost, the term is purely histologic and does not connote a biologic cancerous change in the clinical sense. It is conceivable that prickle cell cancer can occur in hair follicles, whether they are mature or not, but my problem was not concerned with this. As I use the term, a lesion is unequivocally trichoepitheliomatous when hyperplastic cells can be identified in continuity with the sheaths of hair follicles and when such cells have the cytologic characteristics conventionally ascribed to basal cell cancer. This is orthodox thought. After this, the problem resolves itself into establishing proof that the structure concerned is really that of a hair follicle. This, therefore, has occupied the larger part of this study.

Differing from but seemingly related to trichoepithelioma are those structures (hair follicles) the sheath cells of which are hyperplastic but have no cytologic features of basal cell cancer. This may result in the enlargement and deformity of the follicle or even in the suppression of the hair shaft, which will lead to a confusion with genuinely epitheliomatous changes if superficially analyzed. For this type of structure the term hamartoma *(Missbildung)* should be reserved. Obviously, there is not the lawlessness, i. e., neoplastic character and significance, found in hamartoma that is observed in trichoepithelioma. The biologic process is clearly different. Also, these hamartomas that frequently appear as large circumscribed masses of squamous cells enclosing cystic spaces and sometimes surrounded by more or less palisaded basal cells are not to be confused with mixed basal and squamous cell epithelioma or with the so-called basal-squamous transitional type. The malformed hair follicles are composed of mature basal and squamous

24. Stout, A. P.: Human Cancer, Philadelphia, Lea & Febiger, 1932, p. 569.

cells which are distinctly lacking in the anaplastic and invasive characteristics of cancerous growth. The keratinous cysts, which on casual inspection might suggest the pearls of squamous cell epithelioma, after close observation are seen to be lined with several layers of flattened but not anaplastic squamous cells.

The important practical relation that may exist between hamartoma and trichoepithelioma is that common to embryologic vices in general, namely, the superimposition of epitheliomatous changes on a congenital lesion. In this sense, it is fitting to regard the "trichous hamartomas" as members of the precancerous dermatoses, particularly since examples could be found in my sections in which both orders of change were exhibited in the same section. Obviously, both of these histologic abnormalities are to be expected in multiple benign cystic epithelioma, in which there is such ample evidence clinically of not only congenital but hereditary factors.

MATERIALS AND METHODS

The material consisted of histologic sections from lesions in 63 cases, which, for the purpose of correlating the histologic data with the clinical features, will be described under three different headings. Only the data which have an immediate bearing on those phases of the subject which are under study here will be cited.

Group 1: Cases of Clinically Typical Multiple Benign Cystic Epithelioma.—Sixteen cases were included in this group. The lesions were pinhead-sized to pea-sized nodules and were situated chiefly on the forehead, temples, nasolabial folds and root of the nose and in front of the ears. In 1 case the tumors were also present on the scalp.

Histologic sections in 13 of these cases were comparable to those described by Brooke (figs. 1 and 2); the remaining 3 will receive separate notation. In the 13 cases the epidermis was essentially normal except for a moderate degree of hyperplasia in some and pressure atrophy in others. The corium consisted of normal fibrous tissue and contained rounded and irregularly shaped masses of basal cells, some of which were hyperplastic. The interior of most of the cellular masses was occupied by large or small cystic spaces, most of which contained concentrically arranged keratinous material. In some of the smaller cysts this substance was condensed into a circular mass which reminded one of a cross section of a hair shaft. However, in the sections from certain of the cases, hair shafts could be definitely identified in the cystic spaces. The cells immediately lining the cysts, and sometimes several adjacent layers of cells, were flattened and had rather pink-staining cytoplasm and small oval nuclei. In some instances in which these cells were not uniformly alined to the lining of the cyst but extended irregularly outward into the basal cell masses, their outlines became more

Fig. 1.—Multiple lesions on the face (group 1, first 13 cases), illustrating the usual structure of a nodule: keratinous cysts ranging from large to minute, more or less "lined" by apparent basal cell cancer (it is really hamartomatous).

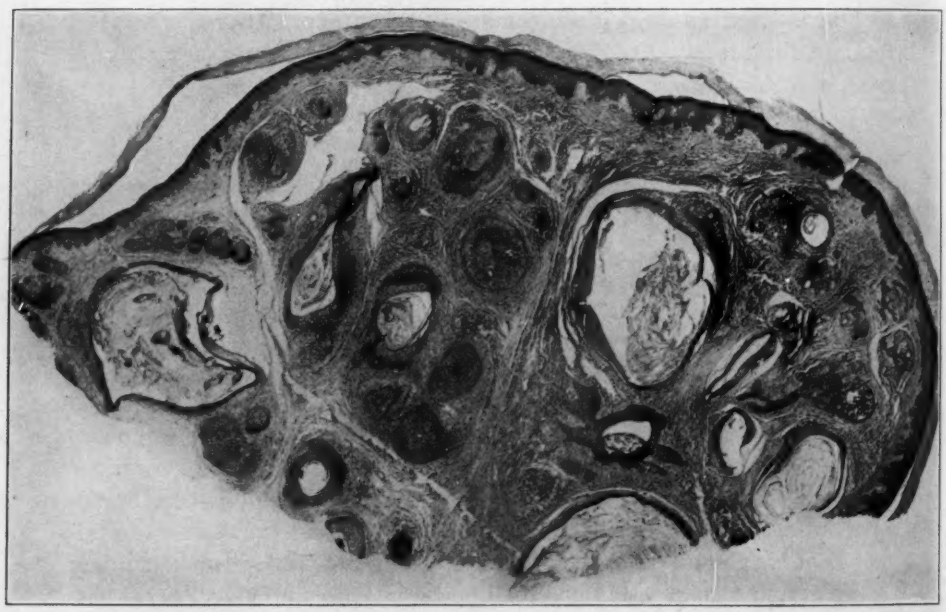

Fig. 2.—Higher power magnification of the more richly cellular foci which are illustrated in figure 1.

oval or cuboidal. In some sections these cells had prickles, whereas in others a prickle type was merely approached. Rarely small clusters of sebaceous cells were associated with such masses of cells. In most of the sections, at some place or other, the cystic complexes or groups of cells were connected with the basal layer of the overlying epidermis. Small foreign body granulomas consisting of lymphocytes and irregular foreign body giant cells were occasionally seen strewn between the larger elements of the tumor.

Fig. 3.—Lesion from the scalp, one of many on the face and forehead (group 1, case 14), illustrating the uniform distribution of varied types of structures, keratinous cysts, Krompecher-like lobules and hamartomatous follicles (in the upper left hand corner).

Within this group there were 3 cases which must be noted separately. In the fourteenth case, that of a 15 year old boy, there was a large lesion on the scalp in addition to the typical lesions of the face. The lesion above the upper lip showed numerous large and small, irregularly shaped lobules of basal cell cancer. The cystlike structures so conspicuous in the preceding 13 cases were indeed scarce; only after search could a few small ones be found. This picture contrasted strongly with the results of examination of the boy's scalp, where cysts were now found. Incidentally, in one location a cylindric strand of cancer cells

was observed to extend down from the basal layer of the epidermis; this suggested a portion of a dermal appendage, e. g., a hair follicle. Hair shafts and sebaceous glands were nowhere identified. Sections from the scalp (fig. 3) showed the epidermis to be thin and atrophic. The corium was almost completely occupied by a definitely circumscribed tumor. The stroma consisted of interlacing bundles of mostly adult, hyaline, keloid-like fibrous tissue. Within it variously sized nests of hyperplastic basal cells were situated; although most of them were comparatively solid, a goodly number were of the cystic type described in the first 13 cases. Definite hair shafts or sebaceous glands were not seen. The particular message from this case was that cystic features can be recessive indeed and may vary within the several lesions of 1 and the same patient.

In case 15 a 12 year girl had lesions distributed about the cheeks, ears, neck and jaws. The microscopic picture of one of the lesions was almost identical with that of the lesion above the upper lip in case 14, i. e., resembling an ordinary basal cell cancer of the Krompecher type. However, a section from another lesion showed a different histologic structure. The epidermis was not notably abnormal. The corium was occupied by a large, well circumscribed mass of cells which was not connected to the overlying rete. The mass at its periphery exhibited the usual characteristics of basal cell cancer, including palisade arrangement of basal cells. The remainder of the cells within the confines of this border had rather broad, pale pink-tinted cytoplasm and plump oval nuclei. Definite prickle cells were plainly visible between almost all of them. There were numerous small liquefaction cysts scattered throughout the tumor mass. No mitotic figures or tendency toward cornification was observed. In no place were the cells seen to invade the connective tissue beyond the limits of the peripheral basal cells. The cellular mass as a whole did not remotely resemble any dermal appendage; nor did most of the cells appear to be of true basal or prickle type. Nothing like this was seen in any of the other cases.

The last case in this group was that of a young man who had a great number of lesions on the face, especially about the nose and around the angles of the mouth. Nine of them were studied microscopically. One (fig. 4) was similar to the Krompecher-like tumors in the preceding 2 cases. There were great masses of solid, rounded and irregular strands of hyperplastic basal cells occupying the corium and extending below the level of the sweat glands but not into the subcutis. Only one medium-sized cyst and two small ones were observed. The latter contained keratinous material and granules of pigment. Alongside of the lesion, and to a lesser extent about it, small underdeveloped hair follicles extended downward from the epidermis; some contained a tiny hair

shaft. No connection between them and the tumor mass was observed. In the lower part of the corium two small sebaceous glands were noted. These did not appear to be associated with any of the cancer lobules.

Sections of the eight other lesions showed a tumor composed chiefly of underdeveloped and atypical hair follicles which contained either hair shafts or keratinous material rolled up so as to resemble a hair shaft. Their cells closely approached the prickle type, with a border of palisaded basal cells—i. e., they were of the order of malformed hair follicles, which nonetheless contained hyperplastic sheath cells. However, this hyperplasia in many follicles was not cancerous, as in basal cell epithelioma,

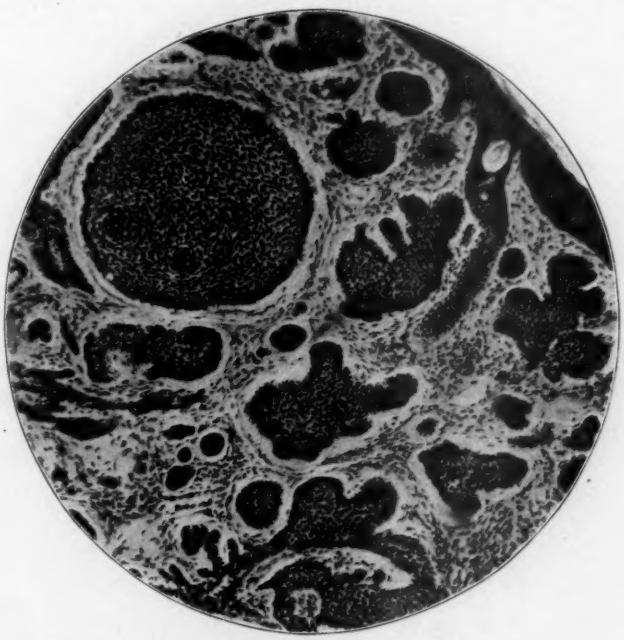

Fig. 4.—One of several lesions on the face of one patient (group 1, case 16). This exhibits Krompecher cancer (i. e., without the "follicular" features). Eight other lesions exhibited hamartomatous features similar to those in figure 1.

but was more in the nature of a hamartoma. Follicles lying deeper in the corium were identical with those extending down from the epidermis. In some sections small sebaceous glands were observed in association with the follicles. In two of these eight lesions the follicles ordinarily occupied by hair shafts were enormously dilated. This gave the tumor a cystic appearance even when viewed without magnification.

Group 2: Lesions Solitary or Scattered, i. e. Not Multiple Benign Cystic Epithelioma Clinically.—Thirty-one cases were classified in this group. In 13 the condition had been clinically diagnosed as basal cell

epithelioma, in 14 as "moles," in 1 as "cylindroma" and in 3 as "undetermined." Slight ulceration had occurred in 3 in which the condition was diagnosed as basal cell cancer.

Histologic sections from a subgroup of 8 cases presented a picture almost identical with that seen in many cases of Krompecher cancer in the sense that the cancer appears to spring exclusively from the basal layer of the epidermis, but still with more or less of a suggestion of abortive attempts at hair follicle formation (fig. 5). Many of the cancerous lobules were elongated into cylinders, which on cross section

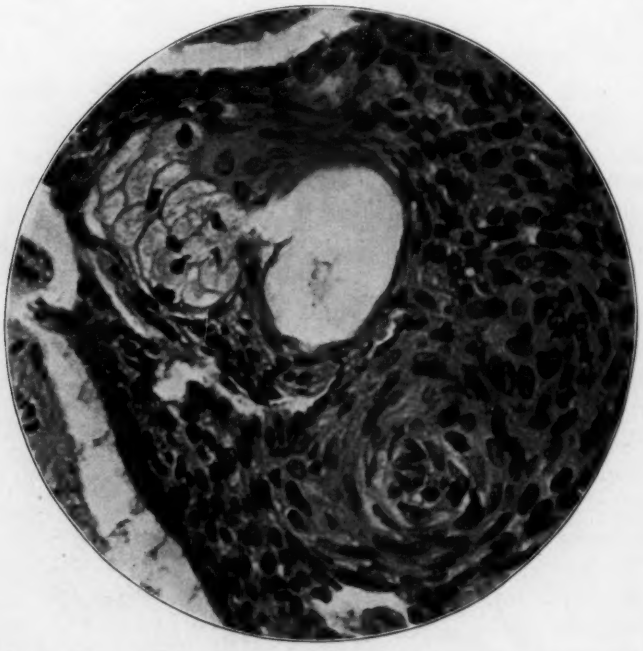

Fig. 5.—A solitary lesion (group 2, first 8 cases), which might ordinarily be regarded as Krompecher cancer, with trichoepitheliomatous features. Such lesions must sometimes be searched carefully before locating fields like this.

revealed the cells to be concentrically arranged into whorls or nests. A few showed slight but definite tendency toward cornification. In the center of some of the smaller nests were minute cysts containing small clumps of brown pigment. The nuclei of the cells at the periphery of the lobules were in palisade formation. In some sections the masses of cells occurred in association with abortive hair follicles and in one section with a minute sebaceous gland lobule. Most of the tumors were fairly well circumscribed and exhibited no disposition to deep penetration. In only 1 instance was there much round cell infiltration in the corium.

In the next subgroup of 9 cases appearances differed slightly and only in degree from the preceding (fig. 6). Cysts were in general larger and more numerous. The cells bordering the cysts were more flattened and had a greater affinity for the acid stain. Moreover, there was a greater tendency toward the formation of keratinous material in the cysts. Hair shafts and sebaceous glands were not seen. Rarely small foreign body granulomas were noted. In brief, the histologic picture here was practically identical with that of the lesions in the first 13 cases previously described in group 1.

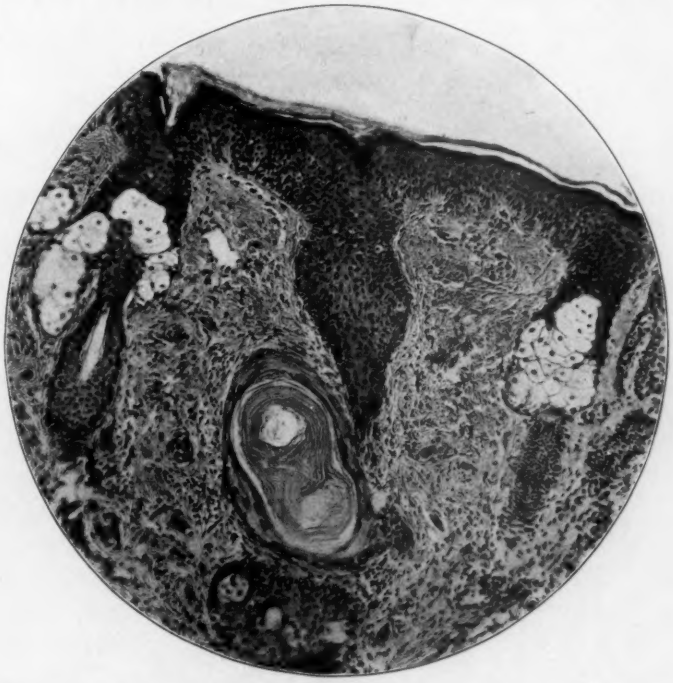

Fig. 6.—A solitary lesion (group 2, subgroup 2), with features similar to those in figure 4 but illustrating keratinous "cysts." The picture is a closer approach to the structure of a hair follicle.

The microscopic appearance of lesions in the remaining 14 cases of this group was much the same as in the last patient of group 1 (eight of the nine lesions); that is, the structures comprising the tumor were incompletely developed but definite hair follicles (fig. 7). Some were considerably distorted by varying degrees of basal cell hyperplasia of their sheaths. Hair shafts were frequently seen, although some of the follicles contained merely keratinous material. In some instances small hair shafts could be detected in the center of a parakeratotic mass in the

follicle. In many follicles the cells between the central space and the peripheral basal cells were definitely of the prickle type, and keratohyaline granules occurred in those bordering the hair shaft space. In 4 of these cases there were cystic dilatations of the follicles. Although occasionally buds of cells extended outward from some of the hyperplastic follicles, there was no sign of deep permeation or invasion. Here, too, the hyperplasia of many of the follicle sheaths impressed one as being of the order of a hamartoma rather than of actual cancer.

Group 3: Clinical Data Not Available.—Sections taken in the 16 cases of this group are of significance only in that the histologic pictures

Fig. 7.—A solitary lesion (group 2, subgroup 3). The basal cell hyperplasia is occurring around an indisputable although distorted hair follicle; the process is hamartomatous.

so closely paralleled those seen in groups 1 and 2. Here again more or less hyperplastic hair follicles were seen in all stages of development. The lesions in 5 cases showed a microscopic picture of Krompecher cancer, but with strongly suggestive trichoepithliomatous features; in 6 the lesions were of the Brooke type, and in 4 there were mildly hyperplastic follicles of the hamartoma type, as in groups 1 and 2.

Two sections from 1 patient were particularly interesting in that one showed the features of a Krompecher tumor with only a hint of hair follicle formation, whereas the other was that of a classic epithelioma adenoides cysticum.

COMMENT

It is clear that, although all of the 16 patients in group 1 presented the typical clinical picture of epithelioma adenoides cysticum (Brooke), the histologic features in regard to attempts at hair follicle formation showed considerable variation. For example, the Krompecher-like type of cancer, showing only a hint of follicle formation (the lesion of the face in case 14 and the first lesions mentioned in cases 15 and 16), may be contrasted with the almost mature type of hair follicle exhibited in eight other lesions in case 16. Between these two extremes is the histologic picture usually regarded as typical of the Brooke tumor and exhibited in the first 13 cases in group 1. Thus, all gradations of attempt at hair follicle formation can be visualized from a primitive embryonal structure, such as an epithelial bud, to an almost fully differentiated dermal appendage.

Further and highly important evidence to support the idea that the histologic differences in these lesions represent merely variations in degree of maturity lies in the occurrence of such variation in separate lesions in the same person. To illustrate, one tumor in case 16 was microscopically similar to a Krompecher cancer, while a lesion from the face showed an almost mature type of hair follicle nevus. Especially significant in this regard was case 14, in which the facial lesion presented a more primitive (Krompecher-like) morphologic picture but the tumor on the scalp, except for its large size and keloid-like stroma, was typical of the Brooke type; if regarded from the point of view of hair follicle development, the lesion of the face and that of the scalp were fundamentally the same, there being only a difference in degree of differentiation. Incidentally, Adamson,[25] Watanabe[26] and Stillians,[27] as well as Dubreuilh and Auché,[28] also observed participation of the hair follicles in their cases of so-called "cylindroma" of the scalp. In addition, Savatard,[29] Biberstein,[30] Scheurmann and Weber[31] and

25. Adamson, H. G.: Multiple Benign Basal Cell Epithelioma of the Scalp, Brit. J. Dermat. **30**:130, 1918.

26. Watanabe, J.: Ueber das Cylindrom und das Epithelioma adenoides cysticum, Arch. f. Dermat. u. Syph. **140**:208, 1922.

27. Stillians, A. W.: Nevo-Epithelioma Adenoides (Cylindroma) of Scalp, Arch. Dermat. & Syph. **27**:481 (March) 1933.

28. Dubreuilh, W., and Auché, B.: Epithéliomes bénins multiples du cuir chevelu, Ann. de dermat. et syph. **3**:545, 1902.

29. Savatard, L.: Epithelioma Adenoides Cysticum, Brit. J. Dermat. **50**:333 (July) 1938.

30. Biberstein, H.: Epithelioma adenoides cysticum in Gesicht und Cylindrome am behaarten Kopf, Arch. f. Dermat. u. Syph. **142**:428, 1933.

31. Scheurmann, H., and Weber, K.: Beitrag zur Kenntnis der spieglerschen Tumoren (Cylindrome) nebst einigen Bemerkungen zum Epithelioma adenoides cysticum, Arch. f. Dermat. u. Syph. **175**:682, 1937.

Schlammadinger [32] reported lesions of the scalp in patients with multiple benign cystic epithelioma on the face. These observations, however, do not necessarily indicate that all growths that morphologically are turban tumors have this same origin; but, as Binkley [33] has pointed out, fundamentally they are probably all nevoid growths arising from an undifferentiated ectoderm.

In regard to the second lesion studied in case 15 of group 1, I am unable to explain its cytologic significance or to correlate it with observations in any of the other cases. The cells appeared to be somewhat intermediate between basal and prickle type. However, the cellular arrangement and the tumor as a whole did not closely resemble the so-called basal-squamous cell epithelioma as described by Montgomery.[34] It was probably basal cell cancer with vicarious prickle cells.

Studies in the second group of cases clearly demonstrate that tumors exhibiting the same structure as those in cases of clinically typical multiple benign cystic epithelioma frequently occur as solitary lesions. It is likely that these represent clinically aberrant forms (formes frustes) of the Brooke entity. As in group 1, the hair follicle element could be traced from the extremely primitive expression to those almost fully developed. Others have also noted the occurrence of trichoepitheliomatous features in histologic sections from cases of conditions other than the classic Brooke syndrome. Eight of Savatard's patients presented solitary lesions. Ejiri [35] observed cystic rudimentary hair follicles in a plaquelike lesion on the cheek of a 2 month old infant. Ingels [36] demonstrated hair follicle participation in lesions in a case in which the condition bore little clinical resemblance to multiple benign cystic epithelioma. Montgomery [22] has emphasized the occasional histologic resemblance of verruca senilis to trichoepithelioma.

This suggests a broader concept of multiple benign cystic epithelioma in both a histologic and a clinical sense; that is, the clinically typical lesions do not necessarily show the histologic picture usually regarded as classic but can exhibit any degree of development of hair follicle structure. Likewise, lesions which are clinically atypical, i. e., occurring singly, often show the classic histologic changes generally associated with the Brooke tumors.

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32. Schlammadinger, J.: Cylindrom und Trichoepithelioma papulosum multiplex, Arch. f. Dermat. u. Syph. **171**:526, 1935.

33. Binkley, G. W.: Naevus Epitheliomato-Cylindromatosus, Arch. Dermat. & Syph. **37**:289 (Feb.) 1938.

34. Montgomery, H.: Basal Squamous Cell Epithelioma, Arch. Dermat. & Syph. **18**:50 (July) 1928.

35. Ejiri, I.: Ueber das Epithelioma adenoides cysticum Brooke, Jap. J. Dermat. & Urol. **34**:86 (Nov.) 1933.

36. Ingels, A. E.: Epithelioma Adenoides Cysticum with Features of Syringoma, Arch. Dermat. & Syph. **32**:75 (July) 1935.

CONCLUSIONS

1. Most multiple benign cystic epitheliomas are histologically trichoepitheliomas. They may show great variation in degree of differentiation in respect to hair follicle structure. The more mature forms of the latter structures could more properly be designated hamartoma than epithelioma.

2. Some so-called "cylindromas" of the scalp are trichoepitheliomatous.

3. Clinically, trichoepithelioma frequently occurs as a solitary lesion independently of any accepted clinical entity, such as multiple benign cystic epithelioma.

4. Some cancers heretofore regarded both clinically and histologically as Krompecher cancer turn out to be "forme fruste" trichoepitheliomas when studied in the light of the preceding observations and may be reconciled with multiple benign cystic epithelioma.

5. Corresponding to differences in structure of the several layers of the normal hair follicle, the elements in the centers of cell nests of trichoepitheliomas can differ from those in the periphery, which will incline toward palisading. Larger and clearer cells in the centers should not be interpreted as evidence that there is an intermixture of squamous cell cancer with the basal cell type.

ABSTRACT OF DISCUSSION

DR. FRED D. WEIDMAN, Philadelphia: Dr. Traenkle has told how the appearances compared in different lesions. To some extent, different histologic pictures were met, and yet all of the specimens came from the same biologic strains, that is, from brothers and sisters. It seemed reasonable, therefore, to assume that all of the pathologic processes were biologically similar, too, and as a matter of fact, clinically the entities were the same. The conditions were not basal cell cancers; clinically they behaved like multiple benign cystic epitheliomas. That gave a splendid opportunity for reconciling and comparing the biology with the morphology. Too much dependence cannot be placed on the structure in appraising a condition.

Supposing one sees a solitary lesion clinically in which the histologic picture is primarily that of basal cell cancer. What is one going to do to determine whether the prognosis is going to be that of basal cell cancer or that of multiple benign cystic epithelioma? This is the crux, namely, that search should be made for evidence of these keratinous nests. If they are large and conspicuous, there is no difficulty at all; the matter is settled. Such nests indicate a relation with trichoepithelioma and, from that, a benign prognosis. It may be that the nests will be small and may have to be searched for. It may be that one would have to examine sections from different levels of the same paraffin block, and perhaps it would not be a bad policy in all cases of basal cell cancer to examine sections from several different levels of the block, in order to determine the presence or absence of these telltale collections of keratinous material. If they are present, the prognosis is better. If they are not found and if reasonable care has been taken to secure

an examination of different levels—that is, representative positions in the same lesion—then, and then only, may one assume that the diagnosis is basal cell cancer, and therefore the less favorable prognosis must be adduced.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I agree essentially with what Dr. Weidman has emphasized. A few years ago Ingels in a case report demonstrated all types of transitions between epithelioma adenoides cysticum, trichoepithelioma and syringoma (Ingels, A. E.: Epithelioma Adenoides Cysticum with Features of Syringoma, ARCH. DERMAT. & SYPH. **32**:75-85 [July] 1935). I have observed other cases in which there were similar transitions to cylindroma. Nomland reported a case in which the condition clinically resembled multiple benign pigmented nevi but histologically was basal cell epithelioma. Krompecher's concept of a basal cell origin for basal cell cancer is generaly accepted. There is a predilection for involvement of the forehead and nose and inner aspects of the cheek in both malignant and benign types of basal cell epithelioma. McDonagh called attention to the fact that many mammals, especially deer, have specialized hairs in the orbital-facial fold, and explained basal cell epithelioma on the basis of the lack of need of things that are present in the lower animals and on the basis of hereditary cell rests. Glasunow expressed the opinion that basal cell epithelioma on the face commenced in and about the lines of fusion of the embryonic facial processes. Paljtschewsky emphasized that basal cells grow in areas which are well supplied with sebaceous glands and often arise from comedos or nevi. Mallory has always championed a hair matrix origin for all types of basal cell epithelioma. In neither benign nor malignant types of basal cell epithelioma have I been able to demonstrate origin from the hair matrix cells. In the benign types, origin from the outer sheath of the outer hair follicles is frequently demonstrable, and therefore one may speak of trichoepithelioma or of multiple benign cystic epithelioma.

The ordinary basal cell cancer (basal cell in crypts), on the other hand, reveals multiple points of origin from the basal cells of the epidermis. The same may be true in some instances of multiple benign cystic epithelioma and even is applicable to cylindromas. The presentation emphasized the difficulty that one encounters histologically in drawing a line between benign and malignant basal cell epitheliomas and the necessity of having both clinical and histologic evidence in a given case.

DR. HERMAN GOODMAN, New York: It is conceded that the single layer of fetal ectoderm becomes the layer of basal cells, which, through chemical and physical changes, pass through the phases of squamous cells and corneum cells. The variations of the primary ectodermal layer become hair follicles.

With regard to facial blemishes, there are records of no less than thirty-seven supposed different types of lesions which arise from the ectodermal layer. Facial cutaneous blemishes, for the greater part, are harmless clinically. Thousands of people receive treatment at the hands of barbers, beauticians and cosmetologists for such blemishes. Rarely, if ever, is an ill effect reported. It becomes confusing, therefore, to have the terminology of cutaneous cancer or cancer applied as a symptom or as a word in the same paragraph as epithelioma when it is utilized for benign cystic epithelioma.

DR. RICHARD L. SUTTON JR., Kansas City, Mo.: One must not be too certain of the benignancy of benign cystic epithelioma. In 2 cases that I have observed each of the many little tumors after having persisted for a long time in a harmless state has grown, producing a slowly progressive lesion, waxy, translucent and of hazelnut size, making a curious and typical picture. The face is grossly distorted, almost as if by nodular lepromas, with eventual ulceration. In such cases, the thirty or forty progressive basal cell carcinomas at one time are difficult therapeutic problems.

I have observed cases in which a lesion arching over the ear like a linear nevus, preauricular and extending upward, consisting of these little waxy pimples, took on active growth. A mass of skin is removed, including what is thought to be all of the tumor-bearing tissue; a year or two later, at the upper end of the scar, a recurrent growth is removed, and shortly thereafter the same type of lesion occurs still farther up the side of the head.

Carefully questioned, practically all patients who have basal cell carcinomas will state, if they are observant, that the lesion began with a tiny, waxy pimple, which they thought was a blackhead and which they squeezed. Thereafter it grew. The question arises then whether the trauma of squeezing this lesion (which I presume was an epithelioma adenoides cysticum—it answers the description accurately) changed the cell type, or whether it simply translocated cells which were already potentially malignant and placed them in more favorable environmental surroundings, where they could grow.

I think malignancy involves consideration of time and that it is not possible to detect the condition solely by histologic study of dead tissue. It is the prerogative only of the clinician to recognize malignant behavior, and the pathologist's original precept of whether a lesion is benign or malignant is confirmed by clinical observation. Malignancy is not a morphologic state. Many a lesion that histologically looks malignant is not. Some that seem to be benign prove eventually not to be. It is only with the passage of time and by observing the changes in a lesion that one can know whether it is malignant or not.

DR. HERBERT L. TRAENKLE, Buffalo: As Dr. Montgomery pointed out, other changes are frequently seen along with multiple benign cystic epithelioma. A number of cases have been reported in which syringomatous features have been noted along with it.

As to Dr. Goodman's question about the term "epithelioma," I should like to make it clear that the term trichoepithelioma as I was using it did not mean epithelioma in a cancerous sense. These lesions are not malignant. I speak of epithelioma purely as a hyperplasia in a histologic but certainly not clinical sense.

I was really not surprised to see hair follicles in different degrees of development. This is not a new concept. McDonagh described these changes in considerable detail over thirty years ago.

There is just another practical point in regard to this concept which has a bearing on practical diagnosis. These single lesions that occur apart from any typical clinical picture and sometimes show considerable distortion of hair follicles—that is, a hamartomatous picture—are sometimes confused by the general pathologist with combined squamous and basal cell epithelioma. Some time ago a general pathologist asked me to see a slide submitted to his laboratory, a section of skin which he thought probably was a combined basal and squamous cell epithelioma. His slide showed large hair follicles which were so distorted that they would not readily appear to be hair follicles to one who had not been thinking along this line. There were also basal cells surrounding large masses of squamous cells. This picture remotely resembled a combined basal squamous cell epithelioma, but actually it was merely a group of hamartomatous follicles.

STAPHYLOCOCCIC IMPETIGO CONTAGIOSA

STEPHAN EPSTEIN, M.D.
MARSHFIELD, WIS.

Two types of impetigo contagiosa of Tilbury Fox can be differentiated, the streptococcic and the staphylococcic. It is the purpose of this article to present the pertinent facts and some additional evidence for the etiology and epidemiology of staphylococcic impetigo contagiosa.

CLINICAL PICTURE

The clinical characteristics of staphylococcic impetigo are best pointed out by comparison with the streptococcic type.

Streptococcic impetigo (figs. 1 and 2) is characterized by lesions with thick, so-called stuck-on crusts of a yellowish, honey-like or dirty color. The regional glands are not infrequently swollen. The original vesicle of streptococcic impetigo is so short lived that usually it is not observed; however, on the fingers, where the horny layer is thicker, larger persisting purulent blisters appear, so-called whitlows. On the limbs streptococcic impetigo, otherwise a superficial infection of the epidermis, may penetrate into the cutis and produce crusted ulcerations, which are called ecthyma.

Staphylococcic impetigo (figs. 3 to 7) is primarily bullous in character. In contradistinction to the streptococcic form, the blisters in staphylococcic impetigo usually persist for days (fig. 5 *a*). After the bullae have ruptured the lesions of staphylococcic impetigo become covered with thin, flat, varnish-like crusts (fig. 5 *b*). The relation of bullous and crusted lesions in the staphylococcic type varies according to the location and age; in hot climates [1] the bullous type apparently is predominant. In babies and infants, too, staphylococcic impetigo, known as pemphigus of the newborn, usually is bullous in character

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From the Marshfield Clinic.

Read before the Section on Dermatology at the Ninety-First Annual Session of the American Medical Association, New York, June 12, 1940.

1. (*a*) Dohi, K., and Dohi, S.: Zur Klinik und Ätiologie der Impetigo contagiosa, Arch. f. Dermat. u. Syph. **111**:629-646, 1912. This article contains a bibliography. (*b*) Engman, M. F.: Impetigo Contagiosa and Its Bacteriology, J. Cutan. Dis. **19**:180, 1901.

(fig. 6). Another variety of the staphylococcic form is circinate impetigo (fig. 7).[2]

It is not always possible to make a clinical distinction between the two types of impetigo contagiosa. There are cases in which characteristics of both forms or lesions which cannot be definitely identified with either group are exhibited. Some authors,[3] with whom I agree, have stated the belief that there exists one more type of impetigo con-

Fig. 1.—Streptococcic impetigo of the face, with heavy crusts (photograph supplied by Dr. M. Jessner).

2. As a rule this type is of staphylococcic origin; however, circinate forms are also known to occur in streptococcic impetigo, but rarely. (*a*) Sabouraud, R.: Impetigo, in Besnier E.; Brocq, L., and Jacquet, L.: La pratique dermatologique, Paris, Masson & Cie, 1901, vol. 2, pp. 856-914. (*b*) Török, L., cited by Jessner.[10]

3. (*a*) Balmain, A. R.: An Investigation into the Etiology of Impetigo Contagiosa, Lancet **2**:484-487, 1926. (*b*) Jadassohn, J.: Dermatologie, Vienna, Weidmann & Co., 1938, p. 554. (*c*) Sulzberger, M. B.: Dermatologic Allergy, Springfield, Ill., Charles C. Thomas, Publisher, 1940, p. 339.

tagiosa, and this is caused by the combined action of the staphylococcus and the streptococcus. Whether this condition is a primarily mixed infection or whether it is one type of impetigo secondarily infected with the other organism is not known. The general opinion is that the secondary invasion of staphylococci in streptococcic impetigo does not alter the clinical appearance. I, too, cannot remember having ever observed streptococcic impetigo turning into the staphylococcic type. However, I have seen the opposite in several instances, typical bullous staphylococcic impetigo assuming the clinical picture of streptococcic impetigo (fig. 8).

Fig. 2.—Streptococcic impetigo around the mouth, with heavy crusts, some with multiple layers, and no blisters (photograph supplied by Dr. M. Jessner).

The two types which are now recognized as streptococcic and staphylococcic impetigo had been differentiated clinically long before the etiologic question was settled.[4]

Dunn,[4a] in 1863, gave an excellent description of what now is regarded as streptococcic impetigo. Fox,[5] in 1864, depicted not one clinical variety but several; descriptions of both types are found in his

4. (*a*) Dunn, R. W.: On Porrigo, Brit. M. J. **2**:576-577, 1863. (*b*) Dohi and Dohi.[1a]

5. Fox, W. T.: On Impetigo Contagiosa or Porrigo, Brit. M. J. **1**:467, 495, 553 and 607, 1864.

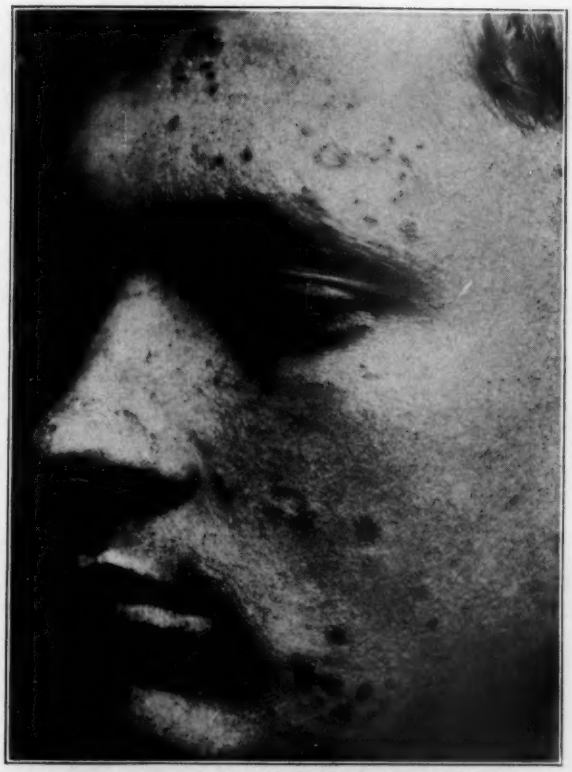

Fig. 3.—Staphylococcic impetigo, with flat crusts and a circinate lesion on the nose.

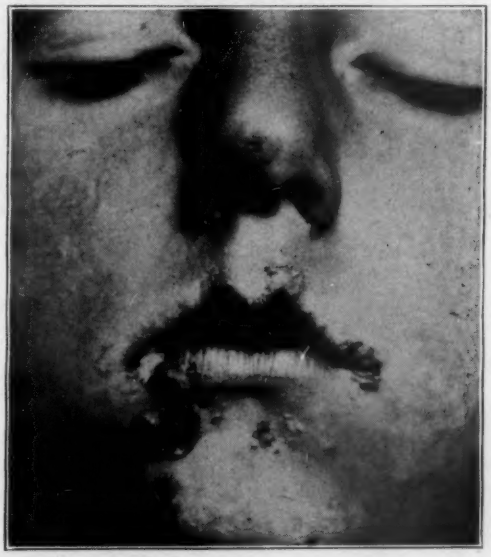

Fig. 4.—Staphylococcic impetigo around the mouth, with flat bullae on the tip of the nose, the upper lip and the chin, with slightly depressed centers.

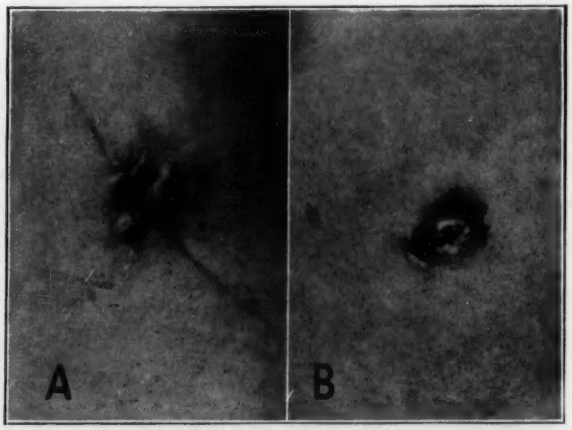

Fig. 5.—*A*, bullous staphylococcic impetigo occurring in scratched skin. *B*, flat crust of staphylococcic impetigo on the cheek (photograph supplied by Dr. M. Jessner).

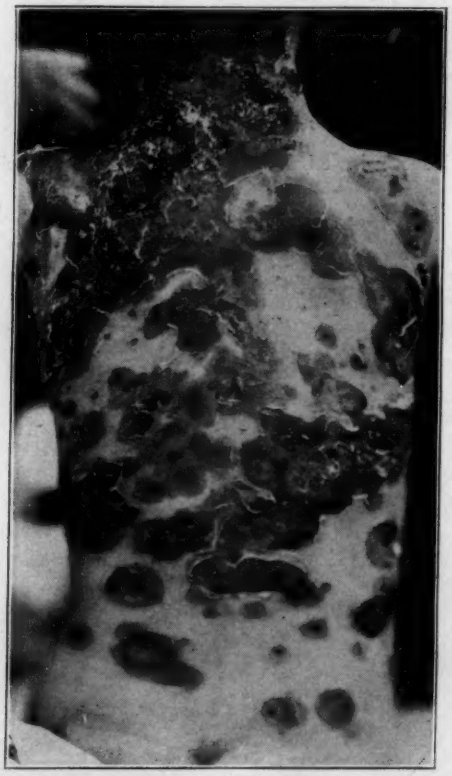

Fig. 6.—Pemphigus neonatorum et infantilis.

papers. His chief description is that of bullous impetigo,[6] which, as is known now, is the staphylococcic form; but he quoted expressly Dunn's description of the stuck-on crust type as a modification of impetigo contagiosa. Engman,[1b] in 1901, differentiated clearly between these forms.

ETIOLOGY

There has been a great deal of confusion as to the causation of impetigo contagiosa of Fox; those who are interested in the historical

Fig. 7.—Staphylococcic circinate impetigo.

development of this controversy must refer to the articles of Sabouraud,[7] Dohi and Dohi,[1a] Lewandowsky,[8] Müller,[9] Jessner[10] and Tachau.[11]

6. According to Fox, the disease looked like a flattened bleb the central part of which was depressed and shrunken; the contents were opaque, while the margin of the bulla, as it now may be termed, was formed by a perfect ring of varying breadth, as though the central part were circumscribed by a collar composed of raised and blistered epidermis and this circumferential ring enlarged pari passu with the bleb.

(Footnotes continued on next page)

The cause of streptococcic impetigo has been settled through the work of Sabouraud [7] and Lewandowsky [8] and is generally accepted. The supporters of the theory of a separate staphylococcic impetigo do not deny the cause of streptococcic impetigo; they maintain only that the streptococcic origin as given by Sabouraud [7] is not the whole story.[12] There is every reason to assume that Sabouraud [13] devoted his studies chiefly to streptococcic impetigo.

The existence of a staphylococic form of impetigo contagiosa is still contested by some authors.[14] It has not been generally accepted

7. Sabouraud, R.: Etude clinique et bactériologique de l'impétigo, Ann. de dermat. et syph. **62**:320 and 427, 1900. This article contains a bibliography.

8. Lewandowsky, F.: Über Impetigo contagiosa s. vulgaris, Arch. f. Dermat. u. Syph. **94**:163, 1909. This article contains a bibliography.

9. Müller, A.: Entwicklung und Stand der Impetigofrage, Zentralbl. f. Haut- u. Geschlechtskr. **25**:385-396, 1928. This article contains a bibliography.

10. Jessner, M.: Impetigo contagiosa und Ecthyma simplex, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1934, vol. 9, pt. 2, pp. 35-158. This article contains a bibliography.

11. Tachau, P.: Pemphigoid der Neugeborenen und Kinder, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1934, vol. 9, pt. 2, pp. 159-234. This article contains a bibliography.

12. Sabouraud clarified the conception of impetigo by clearly separating the staphylococcic folliculitis, or porofolliculitis (unfortunately termed impetigo Bockhart), from impetigo contagiosa of Fox; however, as he failed to recognize the staphylococcic type of impetigo contagiosa, he has been held responsible for the confusion regarding the cause of pemphigus neonatorum (Swendson, J. J., and Lee, S. R.: Impetigo Contagiosa Neonatorum, J. A. M. A. **96**:2085 [June 20] 1931).

13. Sabouraud's descriptions (footnotes 2*a* and 7) are of streptococcic impetigo; all the pictures in his contribution to the Pratique Dermatologique [2a] belong to this type. He stated expressly that circinate impetigo with the flat crusts (which is now considered staphylococcic) was rare. However, this type is frequent when staphylococcic impetigo is abundant (footnotes 1*b*, 10, 17*a* and 17*b*. Grindon, J.: Report of Two Cases of Impetigo Contagiosa, One of Them Fatal, J. Cutan. Dis. **19**:188-190, 1901) but rare when the "stuck-on crust" (i. e., streptococcic) type prevails. Descriptions of other French authors (Besnier, E., and Doyon, A.: Notes, in Kaposi, M.: Maladies de la peau, translated by E. Besnier and A. Doyon, Paris, G. Masson, 1891, p. 674. Brocq, L.: Traitement des maladies de la peau, Paris, Octave Doin, 1892) also indicated the prevalence of the streptococcic impetigo in France at that time.

14. (*a*) Adamson, H. G.: On the Bacteriology of Pemphigus Neonatorum, and a Suggestion for Further Investigation by Different Method of Cultural Proceeding, Brit. J. Dermat. **49**:93-99, 1937. (*b*) Farley, D. L., and Knowles, F. C.: Impetigo Contagiosa, Arch. Dermat. & Syph. **3**:753-758 (June) 1921. (*c*) Fox, H.: Diseases of the Skin in Infancy and Childhood, in Clinical Pediatrics, New York, D. Appleton and Company, 1930, vol. 16, p. 207. (*d*) Milian, G.: Streptococcides bulleuses, in Darier, J., and others: Nouvelle pratique dermatologique, Paris, Masson & Cie, 1936, vol. 4, pp. 95-115. (*e*) Mitchell, J. H.: Streptococcic Infection Simulating Ringworm of the Hands and Feet, J. A. M. A. **104**:1220-1225 (April 6) 1935. (*f*) Sabouraud, R.: Pyodermites et eczémas, Paris, Masson & Cie, 1928.

in America,[15] although the first bacteriologically well founded report about this variety came from Engman [16b] from this country.[16] Most of the modern textbooks do not separate the two clinical entities. The clarification of staphylococcic impetigo is due chiefly to Dohi and his co-workers, to Jadassohn and his school and to Lewandowsky.[17]

BACTERIOLOGY

Staphylococci are regularly cultivated from lesions of staphylococcic impetigo. In America and in Europe the usual type found is Staphy-

Fig. 8.—Mixed impetigo. *A*, impetigo started as circinate bullous lesion beneath the right eye, the remnants of which can still be seen. Typical appearance of staphylococcic impetigo. The subsequent lesions on the cheek and lip were somewhat more infiltrated and atypical. Only a few streptococci were found in the primary lesion, somewhat more in the atypical lesions. *B*, a lesion of the neck, which was the last one to appear, shows the classic appearance of streptococcic impetigo. Many streptococci were found on culture.

15. Wise, F., and Sulzberger, M. B.: Editorial Comment, in Yearbook of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1938, p. 180.

16. The slow recognition of the staphylococcic type of impetigo contagiosa was due chiefly to Sabouraud's erroneous conception that all impetigo contagiosa was

(Footnotes continued on next page)

lococcus aureus, though occasionally Staphylococcus citreus and—as an exception—Staphylococcus albus are found; in Japan the latter is predominant.

The correlation of the clinical diagnosis with the cultural results is given in table 1. It shows that in clinical cases of streptococcic impetigo, streptococci are found in 82 to 96 per cent and in clinical cases of staphylococcic impetigo, staphylococci alone are found in 72 to 85 per cent. That the clinical and bacteriologic diagnoses do not agree completely probably is due to three factors: (*1*) mistakes in diagnosis, (*2*) faulty technic in some cases (the fact that streptococci were cultivated in only 88 per cent of the cases of ecthyma demonstrates this factor) [18] and (*3*) the fact that streptococci can be secondary invaders of staphylococcic infections. This process is demonstrated by the last column of the table, which shows that with the same technic streptococci could be cultivated in 11 per cent of furuncles and axillary abscesses.

TABLE 1.—*Clinical Diagnosis and Cultural Results*

Locality	Clinical Diagnosis	Number of Cases, Total	Streptococci, %	Staphylococci Only, %
Hamburg, Germany (Lewandowsky [17e])	Streptococcic impetigo	184	96	4
	Staphylococcic impetigo	61	15	85
Breslau, Germany	Streptococcic impetigo	113	82	18
	Staphylococcic impetigo	203	28	72
Breslau, Germany	Comparison with:			
	Ecthyma (streptococcic)	43	88	12
	Furuncle and axillary abscesses (staphylococcic)	209	11	89

The ubiquity of staphylococci renders the proof of their etiologic role difficult. It is correct that one is able to cultivate staphylococci from any human skin;[19] but pyogenic, virulent staphylococci are by no

streptococcic in origin. The discussion on Foerster's paper [24a] on impetigo of the newborn, presented in 1909 before the Section on Dermatology and Syphilology, may be cited as evidence of how Sabouraud's authority prevented the acceptance of the staphylococcic origin of this type of impetigo at that time.

17. (*a*) Epstein, S.: Beitrag zur staphylogenen Impetigo contagiosa, Dermat. Ztschr. **70**:328-340, 1935. (*b*) Fuchs, D.: Beiträge zur Frage der Impetigo und des Ecthyma, Arch. f. Dermat. u. Syph. **139**:132-140, 1922. (*c*) Dohi, K., and Kurita: Beitfäge zur Lehre von der Impetigo, Jap. J. Dermat. & Urol. **4**:3-4, 1904. (*d*) Ehrlich, M., cited by Jessner.[10] (*e*) Lewandowsky, F.: Zur Impetigofrage, Arch. f. Dermat. u. Syph. **138**:438, 1922. (*f*) Model, M., cited by Jessner.[10] (*g*) Dohi and Dohi.[18a]

18. These examinations were made routinely by different examiners over many years. Therefore, the results are naturally poorer than those of Lewandowsky,[17e] who made a special personal study.

19. The same is the case with streptococci. Photinos (cited by Milian [14d]) found streptococci on normal skin in 64 per cent, and Jordan (Jordan, P.: Über die Häufigkeit des Vorkommens von Streptokokken auf normaler Haut, Arch. f. Dermat. u. Syph. **159**:152, 1929), in nearly 100 per cent.

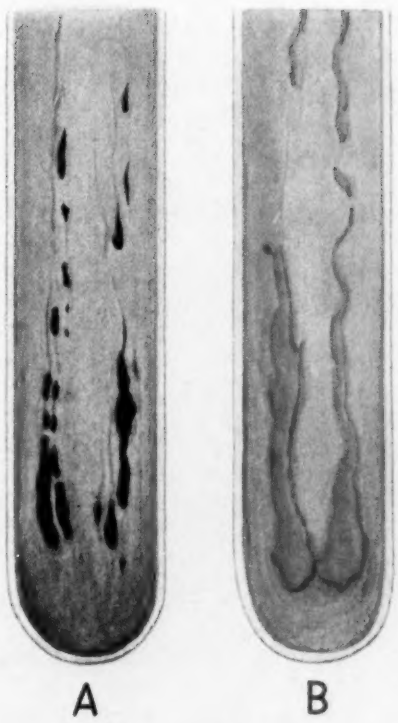

Fig. 9.—Differentiation of staphylococci on crystal violet agar (from Epstein [21]). *A*, group I is hampered in its development, grows in threadlike colonies and takes up the dye. To this group belong the more virulent staphylococci, cultured from furuncles and abscesses. *B*, group II shows more or less normal growth and the original color of the culture. The staphylococci of this group apparently are less virulent. In staphylococcic impetigo, staphylococci of group I as well as of group II are found.

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means regularly found in normal skin or in nonstaphylococcic conditions. Those who studied the staphylococci of staphylococcic impetigo found regularly a virulent pyogenic type.[20]

I have tried, furthermore, to prove the etiologic role of the staphylococci by means of their identification on crystal violet agar. As described in a previous paper,[21] staphylococci transferred to a solid crystal violet medium in proper concentration (1 : 100,000 to 1 : 250,000) present themselves in two groups (fig. 9.). The first group is hampered in its growth, absorbs the dye and appears in blue threadlike colonies. The second group shows more or less normal growth and presents the original yellow or white color of the culture. This behavior is a constant quality of any given strain.[22]

In staphylococcic impetigo either type may be found; however, if the staphylococcus is the cause of this condition, one can expect that

TABLE 2.—*Identity of Staphylococci from Material of Different Lesions of Single Patients and in Epidemics*

	Staphylococcic Impetigo	Streptococcic Impetigo
Total number of cases.....	40	26
Marshfield, Wis.....	15	7
Breslau, Germany.....	25	19
Total number of lesions examined by cultures.....	128	66
Result of culture on crystal violet agar	Identical strains of staphylococci in cultures from different lesions of the same patient or of the same epidemic were found:	
	In all 40 cases:	Only in 8 out of 26 cases:
	In 14 cases a group I (blue), and in 26 cases a group II (orange) staphylococcus was cultured	Staphylococci of different types were found in the other cases

the staphylococci cultivated from various lesions of the same patient or from different patients of the same epidemic all belong to the same group. This need not be the case in streptococcic impetigo, in which the staphylococcus is only a secondary invader. The results of such a study are presented in table 2; they bear out what was anticipated.

20. Aochi, M.: Bacteriological Studies of Impetigo: II. Impetigo Albostaphylogenes Dohi and Impetigo Bockhart, Acta dermat. **10**:301-318, 1927. Epstein.[17a] Dohi and Dohi.[18a]

21. Epstein, S.: Untersuchungen über die Unterscheidung der Staphylokokken bei den verschiedenen Staphylokokkenerkrankungen der Haut, Arch. f. Dermat. u. Syph. **170**:586-601, 1934.

22. (*a*) Biberstein, H.: Bakteriologische Einleitung zu den Pyodermien, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1934, vol. 9, pt. 2, pp. 1-28. This article contains a bibliography. (*b*) Muramoto, G.: Ueber eine neue Differenzierungsmethode von Staphylokokken (Epsteinsches Phänomen), Jap. J. Dermat. & Urol. **40**:171-172, 1936; abstracted, Zentralbl. f. Haut- u. Geschlechtskr. **56**:93, 1937. (*c*) Pinetti, P.: Ricerche sugli stafilococchi della cute in condizioni normali e pathologiche: I. Sulla possibilità di differenziare gli stafilococchi patogeni in base al loro comportamento sui terreni al cristalvioletto, Gior. ital. di dermat. e sif. **78**:215-236, 1937. (*d*) Epstein.[21]

EXPERIMENTAL PRODUCTION OF STAPHYLOCOCCIC IMPETIGO

The etiologic role of the staphylococcus has finally been established by inoculation of human beings. Blisters and crusted lesions have been produced frequently;[23] not all experiments have been successful.[24] It has been claimed that these experiments did not result in typical impetigo contagiosa. However, I have been able to produce experimentally typical circinate impetigo by inoculation of a pure culture of Staph. aureus obtained from lesions of circinate impetigo. Figure 10 seems sufficient evidence.

COMMENT

The differentiation of the two types of impetigo contagiosa will help to settle several controversial questions.

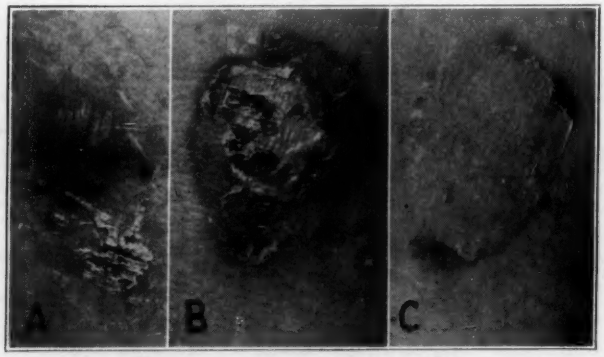

Fig. 10.—Experimental production of bullous staphylococcic impetigo by inoculation of a pure culture of Staphylococcus pyogenes aureus (author's experiment). *A*, bullous lesion appearing on the eighth day. *B*, circinate lesion, after fourteen days; the center is crusted, the edges showing remnants of flat vesicles. *C*, lesion, healing after nineteen days, still shows small vesicle on lower pole. Subculture yielded regularly the original strain in pure culture.

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23. (*a*) Asano, H.: Studien über den Erreger von Impetigo albo-staphylogenes (Dohi), Jap. J. Dermat. & Urol. **37**:782-810, 1935. (*b*) Kaufmann, R.: Untersuchungen zur Ätiologie der Impetigo contagiosa, Arch. f. Dermat. u. Syph. **49**: 297, 1899. (*c*) Kreibich, K.: Zur Eiterung der Haut, in Festschrift gewidmet Moritz Kaposi zum fünfundzwanzigjährigen Professorenjubiläum in Verehrung und Dankbarkeit von Collegen und Schülern, Vienna, W. Braumüller, 1900, p. 400. (*d*) Matzenauer, R.: Zur Frage der Identität des Pemphigus neonatorum und der Impetigo contagiosa, Wien. klin. Wchnschr. **13**:1077-1084, 1900. (*e*) Unna, P. G., and Schwenter-Trachsler: Impetigo vulgaris, Monatsh. f. prakt. Dermat. **28**:229 and 333, 1898. (*f*) Dohi and Dohi.[1a] Engman.[1b] Balmain.[3a] Dohi and Kurita.[17c] Lewandowsky.[17e]

24. (*a*) Foerster, O. H.: Pemphigus Neonatorum, or Bullous Impetigo of the Newborn, J. A. M. A. **53**:358-362 (July 31) 1909. (*b*) Engman.[1b] Balmain.[3a] Epstein.[17a]

1. *Relation Between Impetigo and Pemphigus Neonatorum.*—It has been recognized for some time that pemphigus of the newborn is a staphylococcic infection. The connection of this condition with ordinary impetigo is well known [11] and could not be accounted for by those who insist that all impetigo contagiosa is of streptococcic origin; [25] this relation, however, is easily understood when it is realized that pemphigus neonatorum is nothing but a variety of staphylococcic impetigo.[26]

2. *Impetigo and Age.*—Conflicting reports exist about the incidence of impetigo in relation to age. Table 3 shows that about four fifths of the patients with streptococcic impetigo are children but that only slightly more than one half of the patients with staphylococcic impetigo belong to this age group.

3. *Local Incidence of Staphylococcic and Streptococcic Impetigo.*—It is generally believed that the streptococcic form is more common,

TABLE 3.—*Age Incidence of Streptococcic and Staphylococcic Impetigo*

Locality	Streptococcic Impetigo *			Staphylococcic Impetigo †		
	No. of Cases	Juveniles,‡ %	Adults, %	No. of Cases	Juveniles, %	Adults, %
Marshfield, Wis.	80	82	18	150	56	44
Breslau, Germany (Baer, H., cited by Jessner [10])	173	77	23	144	54	46

* Exclusive of ecthyma.
† Exclusive of pemphigus neonatorum.
‡ Up to and including 16 years of age.

but this is not correct for all localities. The streptococcic type was apparently predominant in Europe, especially in the western part,[27] and in the eastern part of the United States; [9] the staphylococcic type prevailed in Japan. Exact data concerning the occurrence of both types are known only in a few instances. The reports collected in table 4 demonstrate that the relative frequency varies in different regions. The statistics from Breslau, Germany, indicate that this relation may change in the same locality (table 4, columns 4 and 5). The

25. Cole, H. N., and Ruh, H. O.: Pemphigus of the Newborn (Pemphigus Neonatorum), J. A. M. A. **63**:1159 (Oct. 3) 1914. This article contains a bibliography. Milian.[14d]

26. Gandy, D. T.: Bullous Impetigo of the Newborn, Arch. Pediat. **52**:483-488, 1935. Swendson, J. J., and Lee, S. R.: Impetigo Contagiosa Neonatorum, J. A. M. A. **96**:2081 (June 20) 1931. Tachau.[11] Epstein.[17a] Matzenauer.[23d] Foerster.[24a]

27. Flehme, E.: Zur Entstehung der Impetigo, Dermat. Ztschr. **31**:111, 1920. Hiemke, H. J. T.: Untersuchungen über Impetigo vulgaris und verwandte Erkrankungen, Arch. f. Dermat. u. Syph. **170**:123-142, 1934. Engman.[1b]

data from Chicago [27a] and Marshfield, Wis., (columns 6 and 7) seem to indicate that staphylococcic impetigo is predominant in the Middle West.

4. *Seasonal Incidence of Impetigo Contagiosa.*—The reports about the seasonal incidence of impetigo contagiosa are conflicting. That staphylococcic impetigo is most common during the hot summer months seems the only well established fact.[28] A study of my cases in Marshfield, Wis., as well as in Breslau, Germany, reveals that the seasonal incidence of the two types of impetigo is different. Staphylococcic impetigo reaches its maximum in summer; the streptococcic type, in the autumn. The graph for Marshfield presents a slight increase in streptococcic impetigo in spring, but the actual number is too small to permit any conclusion. I may mention in this connection that Newman's [29] series—apparently dealing chiefly with the strepto-

TABLE 4.—*Relative Frequency of Staphylococcic and Streptococcic Impetigo in Different Localities*

Location	Author	No. of Cases	Types of Impetigo		
			Staphylococcic, %	Streptococcic, %	Mixed or Uncertain, %
1. Bern, Switzerland	Lewandowsky [6] (1907)	101	1	99	..
2. Frankfurt, Germany	Flehme [27] (1920)	55	..	100	..
3. Hamburg, Germany	Lewandowsky [17c] (1922)	284	21	65	14
4. Breslau, Germany (1918-1920)	Fuchs [17b] (1922)	258	16	84	..
5. Breslau, Germany (1928-1932)	Epstein	363	52	30	18
6. Chicago	Tachau [29a] (1938)	...	60-70	..	..
7. Marshfield, Wis. (1937-1939)	Epstein	229	58	30	12

coccic variety—presents two maxima, one in late autumn and the other at the beginning of the year. The summer peak of staphylococcic impetigo usually is attributed to heat and perspiration.[30] The maximum of the streptococcic type coincides, according to Newman,[29] with that of streptococcic infections in general. Jausion and Pagès [31] attributed the frequent occurrence in the autumn to photosensitization.

5. *Therapy.*—Differences of the two types of impetigo in regard to response to therapeutic measures may be mentioned. Ointments, such as those containing ammoniated mercury, are well suited for strepto-

27a. Tachau, P.: The Bacteriology of Impetigo Contagiosa, Brit. J. Dermat. **50**:113-118, 1938.

28. Dohi and Dohi.[1a] Engman.[1b] Jessner.[10] Epstein.[17a]

29. Newman, J. L.: Impetigo Contagiosa, Its Epidemiology and Control, J. Hyg. **35**:150-159, 1935.

29a. Tachau, P.: The Bacteriology of Impetigo Contagiosa, Brit. J. Dermat. **50**:113-118, 1938.

30. Cornbleet, T., in discussion on Bazett, H. C.: Effect of Temperature on Skin: Review, J. Invest. Dermat. **1**:413, 1938.

31. Jausion, H., and Pagès, F.: Les maladies de lumière et leur traitement, Paris, Masson & Cie, 1933.

coccic impetigo,[32] but they fail frequently in the treatment of staphylococcic impetigo.[33] Drying lotions and gentian violet solution [34] are superior for this type. Sulfanilamide, efficient in cases of severe or prolonged streptococcic or mixed impetigo, is apparently less effective —if it is effective at all—against the purely staphylococcic form of the disease.

SUMMARY

Staphylococcic impetigo represents a specific entity with a characteristic clinical picture.

The cause of this type of impetigo has been definitely established in the following manner:

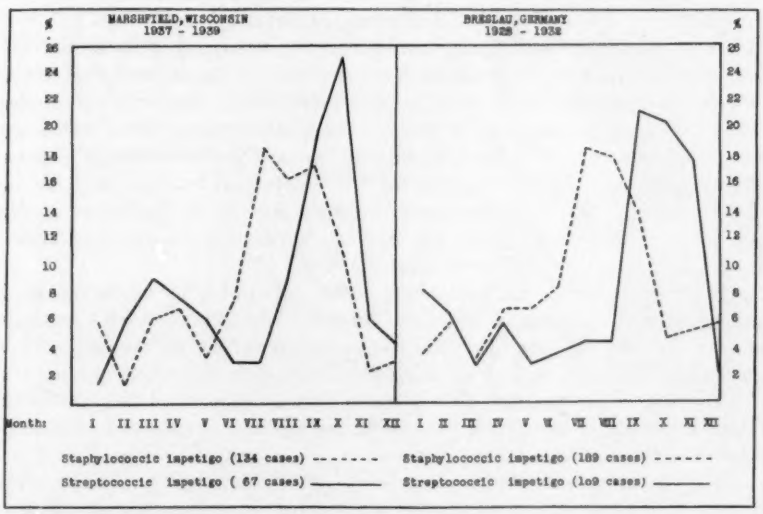
%
MARSHFIELD, WISCONSIN
1937 - 1939
BRESLAU, GERMANY
1928 - 1932
Month: I II III IV V VI VII VIII IX X XI XII
Staphylococcic impetigo (124 cases)
Streptococcic impetigo (67 cases)
Staphylococcic impetigo (189 cases)
Streptococcic impetigo (109 cases)

Fig. 11.—Seasonal incidence of staphylococcic and streptococcic impetigo contagiosa.

1. Correlation of clinical and bacteriologic diagnosis.

2. Proof of the etiologic role of the staphylococcus by special bacteriologic methods.

3. Production of typical staphylococcic impetigo by inoculation of Staph. aureus.

Staphylococcic and streptococcic impetigo differ as to age groups, locality and seasonal incidence.

32. Smith, D. T., and Burky, E. L.: Impetigo Contagiosa in Children: Its Etiology and Treatment, Bull. Johns Hopkins Hosp. **35**:78-81, 1924.

33. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, St. Louis, C. V. Mosby Company, 1939.

34. Sutton, R. L., Jr.: Gentian Violet as a Therapeutic Agent, J. A. M. A. **110**:1733-1738 (May 21) 1938. Smith and Burky.[32]

ABSTRACT OF DISCUSSION

Dr. Marion B. Sulzberger, New York: The concept that there are two forms of impetigo is not original with Dr. Epstein, and he does not pretend it to be such. This work, which I saw him inaugurate in Breslau, Germany, was a continuation of the studies in that clinic by Lewandowsky and by Jadassohn. It might be interesting to hear how this problem was approached in the Jadassohn Clinic. First, every patient with impetigo who came into the clinic was carefully described clinically. The different sites were all examined, and a record was kept of the appearance of the individual lesions, of the course, of the rate of healing and of the residua after healing (such as pigmentation and erythema).

At the first examination the assistants and the chief each expressed an opinion as to whether the impetigo was staphylogenic or streptogenic or mixed, and a record was made of these opinions. It was remarkable to find that after a while there was almost always unanimous agreement among the members of the staff as to whether a condition was staphylococcic or streptococcic or mixed.

After the record of these opinions had been made, the material from the lesions was cultured on a variety of mediums. Then the opinions, based on clinical appearance, were checked against the result of the culture study. It was only after years of work of this kind, in which it could be demonstrated that there was a high degree of agreement between the clinical diagnosis and the bacteriologic diagnosis, that it was decided that in all probability there were two forms—a decision supported by the facts that with experience one could differentiate by mere inspection between one form and the other and that this differentiation then coincided, to the highest degree, with the bacteriologic findings.

Dr. Epstein, of course, has gone much further into this proof of the differentiation between the two forms of impetigo. He has really fulfilled Koch's postulates. That is to say, he has found that one can recover a certain micro-organism from a certain type of lesion with great regularity; that with that micro-organism one can reproduce the disease (the characteristic disease from which one had isolated the micro-organism), and that from the lesions of this characteristic disease one can again isolate the same micro-organism.

One would think that this would be sufficient. However, I am not so certain any more that Koch's postulates are sufficient as proof of the etiologic role of an agent. The point is this: I believe that many micro-organisms and viruses must today be considered as being ubiquitous and saprophytic or quiescent under normal conditions. Then, depending on what method is used to recover them, depending on what precise direction attention is fixed and on what is the principal objective of the study, one or another micro-organism can be recovered from one and the same disease or lesion,. and the disease can be reproduced with that micro-organism by applying it to the skin. One can reproduce that lesion because the other micro-organisms are already present there. In other words, to be specific, if one uses the Griffon-Balzer method of culturing material removed from the skin or from cutaneous lesions, one can find streptococci in practically every cutaneous lesion and in practically any normal skin. If one uses methods and mediums suitable for fungi, one can find cryptococci, pityrospora, monilias, yeasts or yeastlike organisms in practically any skin or any cutaneous lesion. If virus culture medium is used, herpetic virus can be recovered and probably other viruses from almost every cutaneous lesion. Thus, in a lesion such as that of impetigo contagiosa one is likely to find three or four different micro-organisms and viruses, and by damaging the skin and reapplying those micro-organisms one may be able to reproduce the disease, despite the fact that the particular agent inoculated was not

the sole etiologic agent. The same reasoning applies to the lesions of perlèche and of many other dermatoses. However, I believe that in this presentation Dr. Epstein has now brought as conclusive proof of the existence of a staphylogenic impetigo as any one today can demand.

Dr. Richard S. Weiss, St. Louis: I wonder if Dr. Epstein has repeated the early, original work of Engman Sr. on the mutation of the organisms that are found in impetigo. Engman observed that by varying the hydrogen ion content of his culture medium he could make the organism which he recovered from the lesions of impetigo grow as a staphylococcus or as a streptococcus. When his report and his results are considered, one wonders sometimes if some of the patients with so-called streptococcic impetigo might not, after all, have staphylococcic impetigo in which the organism by some change in the skin has been induced to grow as a streptococcus.

Dr. Stephan Epstein, Marshfield, Wis.: Dr. Sulzberger has clarified many of the points in discussion.

Dr. Weiss's question I may answer as follows: I have tried again and again in many different ways to change the two types of cocci one into the other, with no success. I assume that in the early work, around the beginning of this century, some authors might have worked with mixed cultures with which some medium brought out the streptococci and another the staphylococci.

PSEUDOEPITHELIOMATOUS HYPERPLASIA

LOUIS H. WINER, M.D.
MINNEAPOLIS

Pseudoepitheliomatous hyperplasia in chronic inflammation has long been difficult to diagnose. Competent pathologists have occasionally been surprised by the spontaneous healing of a lesion which they had diagnosed squamous cell carcinoma microscopically. The result is that some pathologists have taken the stand that a lesion of this type is a carcinoma only if it is not a specimen from an ulcer on the leg or if it is not associated with chronic granuloma.

In order that the difference between pseudoepitheliomatous hyperplasia and true epithelioma can be appreciated, one must consider the diagnostic characteristics of each.

Borrmann [1] wrote that in early epithelioma of the skin there is a definite transformation of the cutis, which is correlated with and even precedes the invasion by the acanthotic epidermis. Therefore, the changes in the cutis may not be considered a result of epithelial hyperplasia. Ribbert [2] thought the downward growth of epithelium and the epidermal pegs resulted from the failure of the epidermal glands to excrete their metabolites, which caused a solution of the cutis resulting in cavity formations. The epidermis, being in a constant state of proliferation normally, promptly fills these cavities. He diagnosed as squamous cell carcinomas all specimens in which there was a downward growth of epithelium into the connective tissue in the form of elongated rete cones, where finally pearl formations occur. Ribbert [3] stated the belief that subsequent to the epidermal hyperplasia, there was a hyperplasia of the connective tissue, which separated the proliferating epidermis from its matrix, making it independent of the surface epithelium.

Read before the Section on Dermatology at the Twentieth Annual Session of the American Medical Association, New York, June 13, 1940.

From the Department of Dermatology and Syphilology, University of Minnesota, Dr. H. E. Michelson, Director, and the Department of Dermatology and Syphilology, Minneapolis General Hospital, Dr. S. E. Sweitzer, Chief.

1. Borrmann, R.: Entstehung und Wachstum des Hautkarzinoms, Ztschr. f. Krebsforsch. **2**:1-170, 1904.

2. Ribbert, H.: Zur Kenntnis des Karzinoms, Deutsche med. Wchnschr. **32**: 1693-1694 (Oct. 18) 1906.

3. Ribbert, H.: Das Karzinom des Menschen: sein Bau, sein Wachstum, seine Entstehung, Bonn, Friederich Cohen, 1911, pp. 492 and 496.

Heiberg,[4] attempting to find more definite criteria for correct diagnosis in carcinoma, studied the relative nuclear size in the epithelial cells. Although he observed decided variations in the nuclear size, the averages bore out his conclusion, that the presence of very large nuclei ruled out pseudoepitheliomatous hyperplasia but the presence of small nuclei did not rule out carcinoma. Fischer[5] stated the opinion that Heiberg's nuclear measurements ought to be made routine for all tissues. He admitted, however, that not all squamous cell carcinomas can be diagnosed as such by a pathologist, as there is no single specific criterion for the diagnosis of carcinoma. This fact had first been proposed by Ewing,[6] who stated that no single microscopic feature and no combination of occasional observations can be claimed as invariably pathognomonic of cancer. MacCarty[7] studied fresh, unfixed and unembedded tissue, surgically removed, both stained and unstained. Contrary to the conception expressed in many textbooks, that cancer cells were irregular in shape and had asymmetric mitotic figures and pyknotic nuclei, he reported that carcinoma cells were large ovoids or spheroids the nuclei of which contained one or more large nucleoli. The nucleoli were larger in a carcinomatous cell than in a normal cell. He emphasized the need for the examination of fresh unfixed tissue, utilization of the nuclear-nucleolar ratio and high power microscopic examination of the cells.

Another feature which has been considered as essential for the diagnosis of squamous cell epithelioma is dissolution of the epidermal-cutis junction. Montgomery[8] and Broders[9] have proved that the essential feature is not the obliteration of this boundary line but rather the changes within the individual cells of the bordering epidermis. These changes occur by a process of differentiation in which a nonmalignant cell changes into a malignant cell. This process was first called anaplasia by Hansemann.[10] The changes are: increased avidity of the nuclei for basophilic dyes, increased size of the nuclei (both actual and in relation

4. Heiberg, K. A.: Studien über Haut-Epithel-Atypie bei Krebs-und Granulationsgewebe und die diagnostische Verwendung der Kerngrösse, Virchows Arch. f. path. Anat. **234**:469-480, 1921.

5. Fischer, W.: Histologische Diagnose der bösartigen Geschwülste, Med. Klin. **31**:969-972 (July 26) 1935.

6. Ewing, J.: Neoplastic Diseases, ed. 2, Philadelphia, W. B. Saunders Company, 1922, p. 465.

7. MacCarty, W. C.: Identification of the Cancer Cell, J. A. M. A. **107**:844-845 (Sept. 12) 1936.

8. Montgomery, H.: Basal Squamous Cell Epithelioma, Arch. Dermat. & Syph. **18**:50-73 (July) 1928.

9. Broders, A. C.: Carcinoma in Situ Contrasted with Benign Penetrating Epithelium, J. A. M. A. **99**:1670-1674 (Nov. 12) 1932.

10. Hansemann, D.: Ueber assymetrische Zelltheilung in Epithelkrebsen und deren biologische Bedeutung, Virchows Arch. f. path. Anat. **119**:299-326, 1890.

to the cell cytoplasm) and frequently the formation of tumor giant cells due to atypical or pathologic mitosis. Montgomery further emphasized the importance of individual cell keratinization as a characteristic of

Section of a chronic leg ulcer showing grade III pseudoepitheliomatous hyperplasia. Note the pearl formation and deep penetration.

squamous cell epithelioma. Individual cell keratinization occurs either within the epidermis itself or within the independent epidermis in the

cutis. Here the cell loses its intercellular bridges; its cytoplasm becomes more acidophilic, and the nuclei shrink in size or are completely destroyed. Cells so affected are unable to undergo mitotic division. However, the presence of numerous mitotic figures in the stratum spinosum is suggestive of squamous cell epithelioma.

In view of these facts, one can readily realize the difficulty of making a microscopic diagnosis, and one can appreciate why so many investigators have been perplexed by pseudoepitheliomatous hyperplasia in the various granulomas, ulcers and verrucous processes.

The granulomas of the skin which have caused pseudoepitheliomatous hyperplasia are tuberculosis, syphilis, deep ringworm infection, actinomycosis, sporotrichosis and blastomycosis. One of the earliest reports on pseudoepitheliomatous hyperplasia was by Unna [11] in a case of lupus vulgaris. Subsequently Miyahara [12] and Koch [13] reported on microscopic sections from lupus vulgaris and scrofuloderma which showed epithelial hyperplasia. Miyahara stated that some of these changes might be precursors of epithelioma.

Syphilitic lesions, such as chancre, condylomata lata and the late ulcerative or gummatous lesions have frequently shown pseudoepitheliomatous hyperplasia. In addition, however, these lesions have also shown the vascular and infiltrative changes of syphilis and have promptly healed under antisyphilitic therapy. Touraine [14] presented before the French Dermatologic Society a patient in whom a squamous cell epithelioma at the inner canthus of the eye healed under antisyphilitic therapy. In the discussion, Gougerot, who was present, called the condition a pseudoepithelioma, whereas Civatte called it epithelioma. This was, in my opinion, a clear example of pseudoepitheliomatous hyperplasia in a syphilitic lesion. White and Weidman [15] reported 8 cases of pseudoepitheliomatous hyperplasia occurring in deep ringworm infection, gumma of the tongue, furunculosis of the neck and chronic ulcers of the leg. They classified the types of pseudoepitheliomatous hyperplasia into three grades. In grade I, the mildest, there was acanthosis only. Grade II included conditions in which there was a high degree of

11. Unna, P. G.: The Histopathology of the Disease of the Skin, translated by N. Walker, New York, Macmillan & Company, 1896, p. 586.

12. Miyahara, M.: Zur Frage der atypischen Epithelwucherungen beim Lupus und ihrer Beziehungen zum Karzinom, Frankfurt. Ztschr. f. Path. **9**:167-178 (Oct.) 1911.

13. Koch, F.: Zur Frage der atypischen karzinomähnlichen Epithelwucherung, Dermat. Ztschr. **72**:157-161 (Oct.) 1935.

14. Touraine, A.: Régression d'un épithélioma spinocellulaire de l'angle interne de l'oeil sous la seule action du traitement anti-syphilitique, Bull. Soc. franç. de dermat. et syph. **44**:1986-1990 (Dec.) 1937.

15. White, C., and Weidman, F. D.: Pseudo-Epitheliomatous Hyperplasia at the Margins of Cutaneous Ulcers, J. A. M. A. **88**:1959-1963 (June 18) 1927.

acanthosis and excessively irregular epidermal pegs; there was also a rupture of the basement membrane at the epidermis-cutis junction in places where the cells assumed embryonal characteristics with or without pearl formations. Grade III included growths which were definitely epithelioma microscopically but not clinically. The subsequent history revealed that the lesions healed spontaneously and the patients did not show metastases and cachexia.

Their principal criterion for diagnosing epithelioma was the presence of embryonic cells. These cells contained large hyperchromatic, well chromatinized nuclei, and the cytoplasm was more hyaloid, taking a more basic tint than normal and having a more or less rounded contour. In addition, they considered deep penetration of the epidermis into the corium beyond the level of the sweat glands, destruction of the basement membrane and the presence of epithelial pearls. They stressed the importance of considering the microscopic section as a whole and not any one particular feature. Mitotic figures are frequently seen in verrucae, and deep penetration may often be absent in a true squamous cell epithelioma. They concluded that pseudoepitheliomatous proliferation is characterized by the absence of deep penetration, down to or below the level of the sweat glands, and that the clinical observations must be considered at the same time that one studies the histologic sections.

Hollingsworth [16] reported on a patient who had actinomycosis of the dorsum of the hand. After biopsy this lesion was considered a squamous cell epithelioma. The lesion healed completely under conservative surgical excision. Montgomery and Holman [17] reported on a patient with sporotrichosis of the hand which had previously been diagnosed squamous cell epithelioma. The condition in this patient healed completely with the administration of potassium iodide. They also mentioned that in innumerable cases of blastomycosis the condition has been considered epitheliomatous owing to the epithelial hyperplasia. They accepted White and Weidman's classification as to the grading of pseudoepitheliomatous hyperplasia. They expressed the opinion that most pseudoepitheliomatous hyperplasia belonged in group one of White and Weidman's classification and could be diagnosed by the concomitant findings of the dermatosis in question. They also mentioned pseudoepitheliomatous hyperplasia following the use of epithelial stimulants, such as aloe, cysteine and thiocresol, in the treatment of chronic ulcers of the skin. The hyperplastic edges of chronic ulcers and verrucous

16. Hollingsworth, R. S.: Unusual Case of Actinomycosis of the Hand, J. A. M. A. **105**:1266-1267 (Oct. 19) 1935.

17. Montgomery, H., and Holman, J. C., Jr.: Pseudo-Epitheliomatous Hyperplasia in a Case of Sporotrichosis, Proc. Staff Meet., Mayo Clin. **13**:465-469 (July 27) 1938.

lesions, as in bromoderma, which were the most difficult for them to differentiate, were seen to contain numerous mitotic figures in narrow strands of epithelial cells which penetrated deeply into the cutis. They did not see any of the other cellular, nuclear or nucleolar changes usually observed in squamous cell epithelioma.

Characteristic findings in pseudoepitheliomatous hyperplasia of this nature were the invasion of the narrow epithelial strands by leukocytes and the disintegration of some of the epidermal cells, a phenomenon usually not seen in squamous cell epithelioma, although one frequently sees the narrow strands of proliferating epithelium closely surrounded by a dense cellular infiltrate.

Verrucous lesions frequently have pseudoepitheliomatous hyperplasia, as mentioned by Montgomery and Holman.[17] Gougerot, Blum, Bralez, de Vadder and Eliascheff [18] reported on 3 patients in whose cases the clinical diagnosis was verruca vulgaris. They noted that the microscopic sections of these lesions simulated epithelioma owing to the presence of epithelial pearls and also resembled syphilis in that there was a plasma cell infiltrate in the cutis. Goeckerman [19] reported on a patient with a verrucous lesion in bromoderma which on microscopic section showed pseudoepitheliomatous hyperplasia much like that seen in a low grade squamous cell epithelioma.

Levy-Coblentz [20] reported on a patient in whom an ulcer of the arm occurred two months after an injury. The microscopic sections showed proliferation of the epidermal pegs with formation of pearls and the presence of mitosis and atypical cells. However, he considered this simply pseudoepitheliomatous hyperplasia, in view of the rapid evolution and subsequent rapid spontaneous disappearance. Hickel and Oberling [21] had previously presented 2 patients with carcinoma following a single trauma, and the diagnosis was concurred in by Pautrier, who was present at their showing.

Dunn and Smith [22] reported an interesting case of multiple squamous cell epithelioma in which the condition underwent complete spontaneous

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18. Gougerot; Blum, P.; Bralez, J.; de Vadder, and Eliascheff, O.: Lésion naissante de verrucome à structure épithéliomatiforme (sans adénite), Bull. Soc. franç. de dermat. et syph. **37**:1287 (Dec.) 1930.

19. Goeckerman, W. H.: Iododerma and Bromoderma, Minnesota Med. **12**:408-413 (July) 1929.

20. Levy-Coblentz, G.: Pseudo-épithelioma traumatique, Bull. Assoc. franç. p. l'étude du cancer **26**:177-182 (Feb.) 1937.

21. Hickel, P., and Oberling, C.: Epithéliomas cutanés post traumatiques, Bull. Soc. franç. de dermat. et syph. (Reúnion dermat., Strasbourg) **30**:15-20 (Jan.) 1923. Pautrier, L. M., in discussion on Hickel and Oberling.

22. Dunn, J. S., and Smith, J. F.: Self Healing Primary Squamous Carcinoma of the Skin, Brit. J. Dermat. **46**:519-523 (Dec.) 1934.

healing both microscopically and clinically. The only criteria present microscopically were epithelial pearl formations and epidermal proliferation. Montgomery [23] stated the belief that this condition was pseudoepitheliomatous hyperplasia in a case of bromoderma, an opinion with which one can certainly agree.

Spontaneous healing is an interesting phenomenon in the study of the reports of pseudoepitheliomatous hyperplasia. Spontaneous cures of basal and squamous cell epithelioma probably have occurred. The cures have been characterized by complete regression without the influence of any therapeutic curative measures. Touraine and Duperrat [24] have divided the reported cures into three groups, according to biopsy observations: (*a*) single cancerous lesions with epithelioma just beginning to develop, (*b*) single cancerous lesions with partial spontaneous cicatrization of the epithelioma and (*c*) multiple cancerous lesions with a cure of one or more portions.

They mentioned the influence of cellular infiltrate which caused spontaneous cure of tar cancer in mice and rabbits following the cessation of applications of tar. Although this was suggestive, it was not conclusive evidence for the spontaneous cure of cancer in human beings. Slow-growing carcinomas were considered to be relatively benign conditions. They concluded that spontaneous cure of cancer was rare but possible.

This study entails observations on 80 patients, on whom a total of 97 biopsies were made. In 62 of these patients the condition was clinically diagnosed as chronic nonspecific stasis ulcers. In 10 of the 62, pseudoepitheliomatous hyperplasia was present. Also noted in a section of a chronic ulcer of the leg was a basal cell proliferation of the sweat glands and ducts. Of 12 patients with ulceronodular and gummatous syphilis, 6 showed pseudoepitheliomatous hyperplasia, and in 1 a true squamous cell epithelioma was present in the scar. In 4 patients with blastomycosis, proved by the identification of the blastomyces, pseudoepitheliomatous hyperplasia was present. One patient with bromoderma was observed who had pseudoepitheliomatous hyperplasia, and it was also found in a patient with iododerma.

An effort was made to produce pseudoepitheliomatous hyperplasia artificially by the application of 20 per cent aloes ointment. In 10 patients with chronic stasis ulcers the results were negative, while in 1 patient a definite pseudoepitheliomatous hyperplasia was produced which was not present before the applications, as proved by biopsies before and after application.

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23. Montgomery, H.: Precancerous Dermatosis and Epithelioma in Situ, Arch. Dermat. & Syph. **39**:387-408 (March) 1939.

24. Touraine, A., and Duperrat, R.: Guérison spontanée de certains cancers cutanés, Ann. de dermat. et syph. **7**:545-561 (June) 1936.

After a more detailed evaluation of the observations in the sections from leg ulcers, it was apparent that two grades of severity could be recognized, based on the amount of edema present. In the first group, in which the edema was most severe, large intercellular spaces were formed. The edema had disrupted the normal architecture by the formation of large vesicles, but the intercellular bridges, even though stretched, remained present. I did not observe this in my sections of true cancer. It is interesting to note that epithelial pearls were found in the elongated epidermal processes in pseudoepitheliomatous hyperplasia. The epidermal cells had become compressed, the nuclei occupying a relatively larger area than in the normal cell. This was probably due to edema. The columnar arrangement of the basal cells, in places, was disturbed by a dense cellular infiltrate which seemed to be attempting to penetrate the epidermis. The cutis was also edematous and vacuolated. This was especially noticed in the papillary portion, while the reticular portion contained most of the cellular infiltrate.

In the sections from my second group the edema was much more moderate and individual cell keratinization was seen. The same change in the size of some of the epidermal cells was noted. Proliferating epidermal pegs extended down as low as the level of the sweat glands. The basement membrane was intact, and in the cutis the bundles of connective tissue were much denser than normal.

In the sections of the ulcerative syphilitic lesions with pseudoepitheliomatous hyperplasia, the epidermis was seen to be acanthotic and moderately edematous and to contain intraepithelial pearl formations, individual cell keratinization and mitotic figures. The cutis was involved in the papillary layer by a cellular infiltrate of lymphocytes and plasma cells which had replaced the connective tissue. The capillaries were dilated. In the cutis reticularis, the intima of the blood vessels was definitely proliferated and thickened. These vessels were surrounded by a dense mantle of round cells. The connective tissue was barely noticeable in places, owing to the density of this infiltrate.

In the squamous cell epithelioma occurring in the scar of the syphilitic leg ulcer, the intercellular bridges were entirely gone. There were many mitotic figures and many cells with individual cell keratinization. The epidermal cells were much enlarged and closely packed together. There was no intercellular edema. The basement membrane was gone, and there was no pearl formation in the penetrating epidermis. A heavy lymphocytic and fibroblastic infiltrate was present in the cutis. All this is in contrast to the observation in pseudoepitheliomatous hyperplasia.

The blastomycotic sections showed that the epidermis was thickened, especially the stratum spinosum. The basal cells were most involved by the intense edema, which practically obliterated them. The edema

of the epidermis as a whole was considerable. The epidermal pegs, which were greatly proliferated, contained abscesses. Many individual invading cells were seen between the cells of the epidermis. The cutis was entirely invaded by an infiltrate consisting of polymorphonuclear, lymphocytic, fibroblastic and Langhans giant cells.

In the patients with bromoderma and iododerma the intercellular spaces of the proliferating epithelium contained leukocytes.

COMMENT

White and Weidman's classification of pseudoepitheliomatous hyperplasia into three grades lends itself to the microscopic study of the subject. Grades I and II can readily be distinguished. Grade III resembles a squamous cell epithelioma to such a degree that one has difficulty making a correct diagnosis from the histologic sections alone.

The most frequently noticed histologic finding was the edema in the upper part of the cutis and in the epidermis of all the sections which showed pseudoepitheliomatous hyperplasia. The edema caused vacuolation of the intercellular spaces in the lower epidermis and disintegration and vacuolation of the epidermal cells in the upper epidermis.

Although the edema was diffuse, the pseudoepitheliomatous proliferation was, as a rule, localized to a single area. Therefore, the factor of epidermal nutrition must be considered as being a possible cause of pseudoepitheliomatous hyperplasia.

In diagnosing pseudoepitheliomatous hyperplasia in syphilitic lesions, the presence of the characteristic changes in the cutis is a great aid in ruling out cancer.

In tuberculosis of the skin the presence of tuberculoid structure leads to a correct diagnosis.

Usually in fungous infections the clinical observations are so characteristic that confusion rarely exists, while in blastomycosis the finding of epidermal abscesses, the presence of blastomycetes in the section and the coexistence of acute and chronic inflammation are conclusive. Sporotrichosis shows three zones histologically: a central zone, of necrosis containing polymorphonuclear leukocytes; a middle zone, of epithelioid cells, and an outer zone, of lymphocytes and plasma cells. In a case of actinomycosis reported in the literature there was no evidence of actinomycosis in the tissue, but the organism did show on direct smear.

Verruca vulgaris and condyloma acuminatum at times offer real problems in microscopic diagnosis. The hyperkeratosis and parakeratosis, the extreme regularity of the acanthotic process and the intact basement membrane are the differential points.

SUMMARY

Of 62 patients with chronic ulcers of the leg which clinically were not epitheliomatous, 11 had pseudoepitheliomatous hyperplasia. According to White and Weidman's classification, in 7 of these the condition was grade I, in 2 it was grade 11 and in 2 it was grade III. Another had a basal cell epithelioma of sweat gland origin.

Of 12 patients with tertiary syphilitic ulcers, 6 had pseudoepitheliomatous hyperplasia, which was grade I in 2 of them and grade II in 4. A seventh patient had a true squamous cell epithelioma in the scar.

Of the 4 patients with blastomycosis, 2 had pseudoepitheliomatous hyperplasia grade I, 1 had grade II and 1, grade III.

One patient with bromoderma had grade II pseudoepitheliomatous hyperplasia. One patient with iododerma had grade I pseudoepitheliomatous hyperplasia.

CONCLUSIONS

1. Owing to the penetration, although extremely well differentiated cells are seen in pseudoepitheliomatous hyperplasia, it is at times impossible to make a histologic diagnosis. But in most cases a diagnosis can be made by consideration of all the factors present.

2. Spontaneous healing in "epithelioma" means pseudoepitheliomatous hyperplasia.

3. When in doubt, it is best to make several biopsies rather than depend on a single section for diagnosis.

ABSTRACT OF DISCUSSION

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I am in accord with what Dr. Winer has emphasized. I have frequently seen slides from which pathologists have made a diagnosis of epithelioma when actually the condition has been one of pseudoepitheliomatous hyperplasia. This applies especially to Weidman's grade III of pseudoepitheliomatous hyperplasia, in which histologic distinction sometimes is extremely difficult. Grades I and II pseudoepitheliomatous hyperplasia are readily recognized as such.

Some years ago I diagnosed a case as one of grade II squamous cell epithelioma. The diagnosis was confirmed by pathologists at the clinic. Yet the lesion proved to be fungating bromoderma. In this case the cells had penetrated deep into the cutis, and there were many mitotic figures and an attempt at pearl formation. There was also disorderly arrangement of the cells. I have found the following facts of distinct value: In pseudoepitheliomatous hyperplasia there is usually a dense inflammatory reaction of lymphocytes and leukocytes which tend to invade and penetrate narrow or broad strands of epidermal cells that are pushing into the cutis. In true squamous cell epithelioma grades III and IV, the narrow strands of epidermal cells grow deeply into the cutis and may be surrounded by a dense infiltrate, but the tumor cells push the cells of the infiltrate aside and the cells of the infiltrate do not invade and destroy the malignant tumor cells. Furthermore, attention to the character of the nucleus and nucleolus and other features of the

true malignant cell often permits differentiation from true pseudoepitheliomatous hyperplasia, as one sees it in condyloma acuminatum. In the latter condition there is a much more orderly arrangement of the proliferating epidermal cells than is seen in true epithelioma.

Dunn and Smith have reported spontaneous healing of squamous cell epithelioma, but their description and illustrations strongly suggest pseudoepitheliomatous hyperplasia on the basis of a bromoderma. Schurch has emphasized that in experimental carcinoma once definite histologic evidence of malignant change has occurred, involution or a reversible reaction of the precancerous process no longer can occur.

Dr. Fred D. Weidman, Philadelphia: Discussion of this topic can be divided into two parts: first, the academic considerations, and secondly, the practical ones. Little need be said from the first angle. This condition is nothing more or less than a hyperplasia which is in the nature of an attempt at regeneration. Whether the hyperplasia is seen in connection with the sweat ducts, which are surrounded by leukocyte infiltration in a case of erysipelas, or whether it occurs in connection with bacterial infection of the surface epithelium, as in leg ulcers, a fungous condition or a nonviable irritant, as in bromoderma, the principles remain the same. The stimulating substance can be bacterial, fungous or chemical.

Cleveland White and I were prompted to report our experience largely because general pathologists were not aware of the growth capacities of cutaneous epithelium. As I see it, there is probably no epithelium in the body which has the capacities that the skin has in that respect. I wonder whether there is a phylogenetic basis for that, whether a structure of the animal body which for centuries has been exposed to the vicissitudes of environment, as has the skin, has acquired as a matter of evolution a higher capacity for repairing the damages which have been visited on it. The skin is perhaps unique in its capacity for regeneration, and when the stimuli become particularly intense, it is logical to expect that it might react in a more exaggerated way than other tissues of the body.

Turning to the practical angle, I have shown to a number of general pathologists a section from a case which Dr. White was interested in and which could not possibly be one of cancer. Without the history of the case the pathologists rather uniformly diagnosed the condition as squamous cell cancer; it was the grade III pseudoepitheliomatous hyperplasia. I feel that without the clinical history in the case to guide one, there are going to be rather numerous examples of histologic sections which cannot, on a purely morphologic basis, aid in the differentiation between pseudoepitheliomatous hyperplasia and cancer. Grades I and II offer no difficulty; the cytologic picture alone, to the trained histologist, is sufficient to distinguish pseudoepitheliomatous hyperplasia from cancer. But in the grade III type, as I see it, the cytology may be the same in certain cases as squamous cell cancer.

To state the situation in the form of an axiom, whenever one encounters a case with a histologic picture that looks like prickle cell cancer and with the added history that cutaneous epithelium was concerned and that there was a high grade of stimulus, such as suppuration, also existing, one should discount heavily the diagnosis of carcinoma. It is better to wait before employing radical methods of therapy. In short, if there is anything noted clinically that is not consistent with the histologic diagnosis of prickle cell cancer, until it is ascertained by clinical means whether or not the condition will regress by simple, soothing applications, treatment should not be radical.

DR. J. FRANK FRASER, New York: I have encountered a half-dozen cases in which epithelial hyperplasia was mistaken for squamous cell carcinoma. I use the term epithelial hyperplasia in preference to epitheliomatous hyperplasia, because the hyperplasia is not related to carcinoma.

In a case which came under my observation there was a lesion of the tongue which was diagnosed as epithelioma by another pathologist. I found no evidence of malignant changes, and the subsequent history of spontaneous resolution proved the incorrectness of the original diagnosis.

In other cases I have seen epithelial hyperplasia with hyalinization of hair follicles mistaken for pearl formation. These mistakes could be avoided if one would remember that true pearl formation represents an attempt on the part of cancer cells to differentiate into corneous epithelium. A positive diagnosis of cancer finally rests on the presence of the characteristic histologic signs of malignancy, such as disordered polarity, enlargement and irregularities in the shape of the cells, hyperchromatism of the nuclei and mitotic figures.

DR. LOUIS H. WINER, Minneapolis: Regarding the terminology of this condition, I think the original name given by Dr. Weidman is sufficient and explanatory, because it means just what it says, pseudo or false epitheliomatous hyperplasia.

Regarding the lingual lesion mentioned by Dr. Fraser, Drs. Weidman and White in their original article described such a lesion which was diagnosed as a carcinoma and was proved later to be a pseudoepitheliomatous hyperplasia.

As regards the grade III pseudoepitheliomatous hyperplasia, I do not think I can give you any more enlightenment on its diagnosis than to say that if one is on the lookout for such a condition, one will recognize it by its general appearance and the general factors associated with the condition; for example, in syphilis these factors are the associated syphilitic infiltrate and the intimal proliferation of the vessel walls.

MOBILIZATION OF BISMUTH PRODUCED BY AMMONIUM CHLORIDE

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Preparations of arsenic or bismuth are at present the most effective and dependable therapeutic agents for the treatment of syphilis. Therapy by these two drugs is continuously or alternately employed with the object of inflicting the maximum damage to the causative organism with the minimum injury to the body tissues. It is necessary in the case of bismuth to insure a fairly continuous supply of the medicament for effectively maintaining adequate therapy. This is accomplished by regular administration of additional quantities of the drug. Bismuth therapy by this approach leads to retention of the drug in the tissues. Relatively large quantities of retained bismuth are stored in the body when the preparation is employed over a long period in patients resisting a reasonable amount of medication.

It is possible that untoward effects may result from this storage. Cormia [1] called attention to a depressing influence produced by bismuth therapy and manifesting itself by general symptoms, which included fatigue, weakness and loss of weight. He asserted that chronic cough has been listed as a prominent symptom of bismuth intoxication.

Cole, Sollmann and Henderson [2] investigated the bismuth content of the viscera of 22 adults treated with bismuth and of 3 infants whose mothers had received injections of a bismuth preparation. Bismuth salicylate had been most frequently employed in those 25 cases. They reported a median retention of 7.4 per cent of the bismuth administered —a quantity forming the greater part of the unexcreted element. This

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Read at the Sixty-Third Meeting of the American Dermatological Association, Inc., Colorado Springs, Colo., May 30, 1940.

1. Cormia, F. E.: Over-Treatment in Syphilis, Canad. M. A. J. **40**:445 (May) 1939.

2. Cole, H. N.; Sollmann, T., and Henderson, K.: Choice of Bismuth Preparation: Clinical Résumé of Excretion and Retention Studies, Am. J. Syph., Gonor. & Ven. Dis. **23**:143 (March) 1939.

bismuth is to be supplemented by the metallic settlements in the bones and other tissues not investigated by these writers and forms altogether an appreciable amount of the unused material. The bismuth content of the skeleton is, according to Gruhzit, Tendick and Sultzaberger,[3] greater than that of any other part of the body except the kidneys and spleen.

Bismuth and lead have certain points of similarity. They belong to the same series in the periodic system of the elements and agree in various chemical characteristics. One of their outstanding likenesses is their deposition in the skeletal system. From the roentgenologic standpoint the lesions of lead and bismuth have been found identical by Caffey.[4] Moore [5] noted evidences of storage of bismuth in the bones much like the storage of lead. This occurred during the use of both soluble and insoluble preparations of bismuth. It is necessary, in treating lead poisoning, to employ primarily measures for immobilizing the metal in such fashion that tissue damage resulting from its circulation is promptly checked. It is then considered appropriate to inaugurate a regimen to eliminate the element from the body after the acute symptoms of lead intoxication have subsided and other conditions are favorable. This is accomplished by a reversal of the earlier plan and by the use of drugs having a solvent and eliminant effect. This elimination may be effected by the employment of one or other of several means at one's disposal. The agencies generally considered most useful are ammonium chloride, potassium iodide and sodium bicarbonate. These preparations are usually given by mouth. Care is essential in the process of elimination to obviate too rapid streaming out of the lead so that no further damage to the cells is produced.

An interaction between the two metals, lead and bismuth, was recently pointed out by Epstein.[6] He suggested that the administration of bismuth in cases of latent plumbism may displace lead and may produce active symptoms of saturnism during its use as an antisyphilitic agent.

Since bismuth parallels its sister element lead in mode of deposition and elimination, the analogy would be that the former drug should be similarly dealt with and the same reagents be employed with like results. However, an obvious difference exists in connection with the

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3. Gruhzit, O. M.; Tendick, F. H., and Sultzaberger, J. A.: Bismuth Absorption, Distribution and Elimination, Am. J. Syph. **11**:87 (Jan.) 1927.

4. Caffey, J.: Changes in Growing Skeleton After Administration of Bismuth, Am. J. Dis. Child. **53**:56 (Jan., pt. 1) 1937.

5. Moore, J. E.: The Modern Treatment of Syphilis, Springfield, Ill., Charles C. Thomas, Publisher, 1933, p. 114.

6. Epstein, E.: Effect of Bismuth Therapy in Latent Plumbism, Arch. Dermat. & Syph. **41**:38 (Jan.) 1940.

elimination of bismuth and lead, in that on the one hand it is designed merely to rid the body of lead, whereas on the other the therapeutic effect prior to elimination is desired. The value of bismuth therapy appears to become rapidly curtailed after administration of the drug is discontinued, even though considerable amounts of bismuth are still stored in the tissues. It seemed desirable to ascertain whether the retained bismuth could be further utilized and reactivated, at least in part. The gradual release of the stored bismuth for the reactivation of the drug over a period of time might be of value in extending the treatment of syphilis without further introduction of bismuth.

The administration of ammonium chloride by mouth was employed for this purpose. It was our wish in this study to determine the concentration of bismuth in the blood plasma before and during the administration of ammonium chloride, but the results of our chemical examination of the blood of syphilitic patients receiving bismuth therapy were inconclusive. We agree with Cole and those who support him that the amount of excreted bismuth in the urine is a fair index of the actively circulating bismuth. The patients selected for this preliminary report had been treated with bismuth salicylate in oil. In their investigation of various bismuth preparations, Sollmann, Cole and Henderson [7] observed that the salicylate was most apt to be retained, because of the limited absorption from sites of injection. The limited absorption was no doubt due in part to the mechanical difficulty produced by the oil, which prevented absorptive contact. Bismuth obtained in the urine after the administration of ammonium chloride is derived almost entirely from visceral deposits or from areas of injection. Sollmann, Cole and Henderson stated the belief that the "organs retain the stored bismuth with great tenacity and practically indefinitely." It is highly probable that bismuth under these conditions has no detrimental effect on the organism and remains as a nonirritating addition to the body bulk.

Wise and Sulzberger [8] have justly stated: "It is questionable in our minds whether or not rapid distribution and excretion of the intramuscular deposits is a desirable attribute." It must be understood, however, that in the cases reported liberation of bismuth had practically ceased and the deposits of the metal in the body were apparently dead storage areas from which the body unaided could not draw any more remedial effect. It is assumed from roentgenologic studies [9] that the

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7. Sollmann, T.; Cole, H. N., and Henderson, K.: Clinical Excretion of Bismuth, Am. J. Syph., Gonor. & Ven. Dis. **21**:480 (Sept.) 1937.

8. Wise, F., and Sulzberger, M. B.: Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1934.

9. Schrus, H. T.: Ueber die Verteilung der Wismutdepots bei intramuskulärer Injektion unlöslicher Salze und die Dauer der röntgenologischen Nachweises, Fortschr. a. d. Geb. d. Röntgenstrahlen **40**:42 (July) 1929.

gluteal deposits of bismuth may persist for at least two years, a period which makes these deposits the last vestiges for therapeutic activity. It is, however, likely that this gluteal supply seeps into the circulation at a rate which discounts antisyphilitic effect. While additional quantities of the drug could be introduced whenever desirable for continued treatment, it seems more reasonable to free the stored supply by the action of a solvent administered by mouth. The action of the solvent does not apparently involve such a rapid rate of excretion that the kidneys or other viscera are subjected to unusual risk of damage. The bismuth content of the urine during excretion induced by solvent therapy is usually moderate.

Patients were selected for this study from the syphilis clinics of the Jefferson and Pennsylvania hospitals of Philadelphia. Only patients satisfying certain criteria were employed: 1. All patients had received not less than forty injections of bismuth salicylate averaging 100 mg. each. 2. The last injection had been received from four months to four years previous to this study. 3. Roentgenograms of the buttocks showed heavy deposits of the metal, of the "milky way" [9] type for the most part, although occasionally the fanlike appearance was noted. None of these patients had received injections so recently or had deposits so limited in distribution as to suggest the "plumb-bob" shape. These patients, then, exhibited deposits of the drug probably possessing no further significance in so far as therapeutic effect was concerned.

The urine was examined twice on successive days before the administration of ammonium chloride was commenced and proved to give negative results to the rapid test for bismuth according to the method of Hanzlik, Lehman, Richardson and Van Winkle.[10] Exception to this procedure was made in the case of 3 patients who had but one preliminary examination each, with negative reaction. A fourth gave a positive reaction to the initial test, with a negative response the following day. In this last case query revealed that the day before the passage of the specimen of urine the patient had consumed a large quantity of fruit juices.

The results of our studies are shown graphically in the chart.

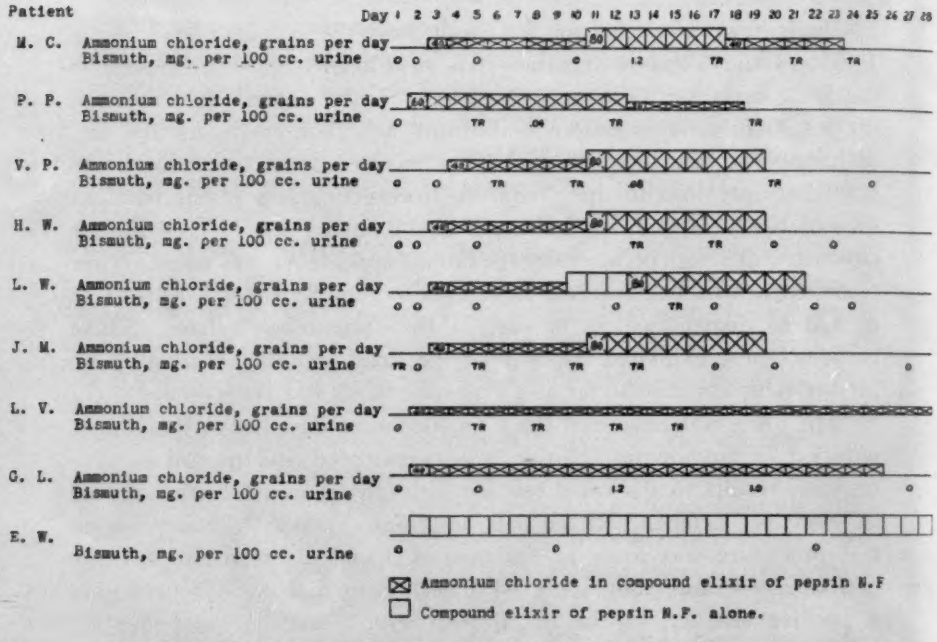
CASE 1.—M. C. did not show evidence of bismuth in the urine while taking 40 grains (2.6 Gm.) of ammonium chloride daily. After taking daily doses of 80 grains (5.2 Gm.) for two days, 1.2 mg. of bismuth per hundred cubic centimeters of urine appeared. Thereafter a trace of bismuth was shown in the urine even when the daily dose of ammonium chloride was reduced to 40 grains.

10. Hanzlik, P. J.; Lehman, A. J.; Richardson, A. P., and Van Winkle, W., Jr.: Rapid Clinical Method for Estimation of Bismuth in Urine, Arch. Dermat. & Syph. **36**:725 (Nov.) 1937.

CASE 2.—P. P. was given daily doses of 60 grains (4 Gm.) of ammonium chloride. He showed a trace of bismuth three days later. On the seventh day 0.04 mg. per hundred cubic centimeters of urine appeared, and a trace was apparent later when the ammonium chloride had been reduced to 30 grains (2 Gm.) a day.

CASE 3.—V. P. showed a trace of bismuth two days after taking daily doses of 40 grains of ammonium chloride, and 0.08 mg. per hundred cubic centimeters appeared in the urine two days after the dose was increased to 80 grains. A trace was again present on the day administration of the drug was discontinued, and six days later no bismuth was found in the urine.

The other patients showed much the same result except that the quantities of eliminated bismuth were smaller.


Patient
Day 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
M. C.
Ammonium chloride, grains per day
Bismuth, mg. per 100 cc. urine
P. P.
Ammonium chloride, grains per day
Bismuth, mg. per 100 cc. urine
V. P.
Ammonium chloride, grains per day
Bismuth, mg. per 100 cc. urine
H. W.
Ammonium chloride, grains per day
Bismuth, mg. per 100 cc. urine
L. W.
Ammonium chloride, grains per day
Bismuth, mg. per 100 cc. urine
J. M.
Ammonium chloride, grains per day
Bismuth, mg. per 100 cc. urine
L. V.
Ammonium chloride, grains per day
Bismuth, mg. per 100 cc. urine
G. L.
Ammonium chloride, grains per day
Bismuth, mg. per 100 cc. urine
E. W.
Bismuth, mg. per 100 cc. urine
Ammonium chloride in compound elixir of pepsin N.F
Compound elixir of pepsin N.F. alone.

Excretion of bismuth in the urine following the administration of ammonium chloride to syphilitic patients who had formerly received bismuth therapy.

Of interest are the reports of 2 cases which should be discussed separately.

CASE 5.—L. W. received by mistake on the tenth day of therapy a bottle of the usual vehicle without the addition of ammonium chloride. His record is included but is probably of less value on account of this error.

CASE 8.—G. L. received daily doses of 40 grains of ammonium chloride. She excreted relatively large amounts of bismuth on two occasions, but this elimination later ceased despite continuation of administration of the drug.

CONTROL CASE.—The control patient, whose record is shown on the chart, received compound elixir of pepsin N. F. without ammonium chloride. His urine contained no bismuth throughout the experiment.

COMMENT

Ammonium chloride increases the secretion of urine by osmotic action. Bischoff found the p_H of the blood was reduced 0.2 by ingestion of 15 to 20 Gm. of the drug. The calcium content of the urine is increased as a reaction of defense against acidosis. The calcium content of the blood is not affected by this loss; therefore, the calcium in the urine is apparently drawn from the bones. Calcium and lead are deposited and eliminated together. Possibly this is the case with bismuth and calcium. The urine of our patients was not tested for calcium for the purposes of this study.

No dietary regulations were suggested to these patients. It is highly probable, however, that such factors are of importance in the mobilization of bismuth through their effect on the p_H of the blood. This is subject to further investigation. Since this study was conducted on dispensary patients who were without close supervision in the matter of regularity and precision of dosage, it is not known in exactly what quantities ammonium chloride was taken. It would seem from observation, however, that there was fairly close adherence to instructions.

Patients were given daily doses (30 to 40 grains) of ammonium chloride in compound elixir of pepsin N. F. When bismuth failed to be eliminated, the dose of ammonium chloride was doubled, bringing about prompt effect in the majority of cases.

SUMMARY

Tolerable doses of ammonium chloride were administered by mouth to a group of patients who, by treatment records and roentgenologic observations, were shown to have deposits of bismuth.

Urinary tests for bismuth which formerly gave negative results gave positive reactions as a result of this medication.

ABSTRACT OF DISCUSSION

DR. HARTHER L. KEIM, Detroit: I should like to ask Dr. Corson if any of these patients were studied with roentgenograms after the administration of ammonium chloride. If so, was there any appreciable diminution in the size of the deposit?

DR. EDWARD F. CORSON, Philadelphia: Dr. Keim's criticism is a proper one and one which I rather expected, because our performance lagged behind the advance abstract of this paper. It was intended to follow up this study by roentgenologic examination of the buttocks. This is still going to be done. Several excellent papers have been written on the subject of the absorption, distribution and excretion of bismuth. To the writers of those papers we are certainly most appreciative for the help they have given.

TRANSVERSE FURROWS OF THE NAILS

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AND
SIDNEY LITTMAN, M.D.
CLEVELAND

Transverse furrows in the nails vary in width and in depth from 1 to several millimeters. They are found traversing a nail from border to border, always parallel to the matrix, in contrast to normal cornified epithelial ridges, which pursue a course parallel to the dorsal surface of the phalanx. We have observed the appearance of these furrows in connection with normal skin on the phalanx and an otherwise intact nail. They occur in the course of metabolic disturbances of the whole organism; they are interesting signs that the organism is a unit. They are valuable as a practical aid in diagnosis. Parisot [1] stated: "The nail and the epidermis are mirrors that truly reflect the metabolic disturbances of fever and the constitutional illnesses of an organism." Reil [2] in 1792 first noted the occurrence of these lines in the course of fevers and observed that they run parallel to the lunula. Beau [3] in 1846 again called attention to these transverse ridges and even considered leukopathia as an equivalent to the transverse furrows.

There are numerous demonstrations in comparative pathology of changes in the horny appendages of the skin following disturbances of nutrition and metabolism. For example, the ring formations of the hoofs of horses are homologous structures. In horses, which suffer from a disease, the height of these ridges and their distance apart from each other have been observed to be indicative of the intensity and the duration respectively of the pathologic process. When the type of fodder available to sheep is altered, there appears [4] a differentiation in their wool. With each subsequent change of food supply a parallel structural alteration occurs in the sheep's coat. During a severe winter

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From the Diabetic and Dermatological Clinics of the Department of Medicine, Mount Sinai Hospital.

1. Parisot, L., cited by Heller.[4]

2. Reil, J. C.: Unguium vitia in convalescentibus a febre maligna observata, in Memorabilium clinicorum medico-practicorum, Halle, lit. Trampianis, 1792, vol. 2, pt. 1; cited by Heller.[4]

3. Beau, J. H. S.: Certains caractères de seméiotique retrospective, présentés par les ongles, Arch. gén. de méd. **2**:447, 1846; cited by Heller.[4]

4. Heller, J.: Die Krankheiten der Nägel, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 13, pt. 2, p. 60.

with an insufficiency of provender, birds demonstrate a diminution in the number of their pin feathers. The same observation has been made on poorly fed captive falcons. With the birth of every calf, a ring develops at the root of both horns of the cow. Similarly, when the pregnant cow is inadequately nourished, the hair of its newborn calf is found to be poorly developed.

Transverse furrows appear after an interference with metabolism. Prolonged fevers, afebrile illnesses and changes in nutrition are some causative agents.

EFFECTS OF CHANGES IN NUTRITION

Transverse furrows have been frequently observed in breast-fed infants. In the transition from fetal to extrauterine life, Schick [5] stated that there is a disturbance of the entire metabolism. This is manifested by the loss of weight during the first days of life. Well developed transverse furrows parallel to the matrix can be observed during the fourth week of life. These furrows, usually most apparent on the thumbs, traverse the entire length of the infant's nail in ninety to one hundred days. All disturbances in nutrition that retard body growth may impair nail growth.

Numerous observers have recorded the appearance of transverse furrows in patients with various pathologic conditions, such as parotitis, scarlet fever and malaria, and in the course of pulmonary infections both acute and chronic, such as pneumonia, influenza and tuberculosis. Most reports concerning the occurrence of transverse furrows have been associated with their incidence following pathologic alterations in the gastrointestinal and biliary tracts, including catarrhal jaundice, icterus gravis, hepatitis, hepatic insufficiency, gastroenteritis, diarrhea of infants, typhoid fever, pellagra and polyneuritis due to arsenical intoxication. During the routine examination of the nails of diabetic persons, these furrows may easily be detected by the distortion of light reflected by the nail or by direct palpation by means of the examiner's finger nail. In this manner the ridges are frequently encountered.

We have noticed that although all nails may participate in this phenomenon, the thumb, index finger and great toe in our series were more prominently affected. In our series the nails were usually symmetrically involved. Our observations do not agree with those of Heller,[6] who stated that transverse furrows do not occur in the course of chronic metabolic diseases. On the contrary, the number of consecutive furrows on any nail demonstrates to us a severe and lasting metabolic imbalance. If the rate of growth of the nail is estimated to

5. Schick, B.: Die physiologische Nagellinie des Säuglings, Jahrb. f. Kinderh. **67**:146, 1908.

6. Heller,[4] p. 70.

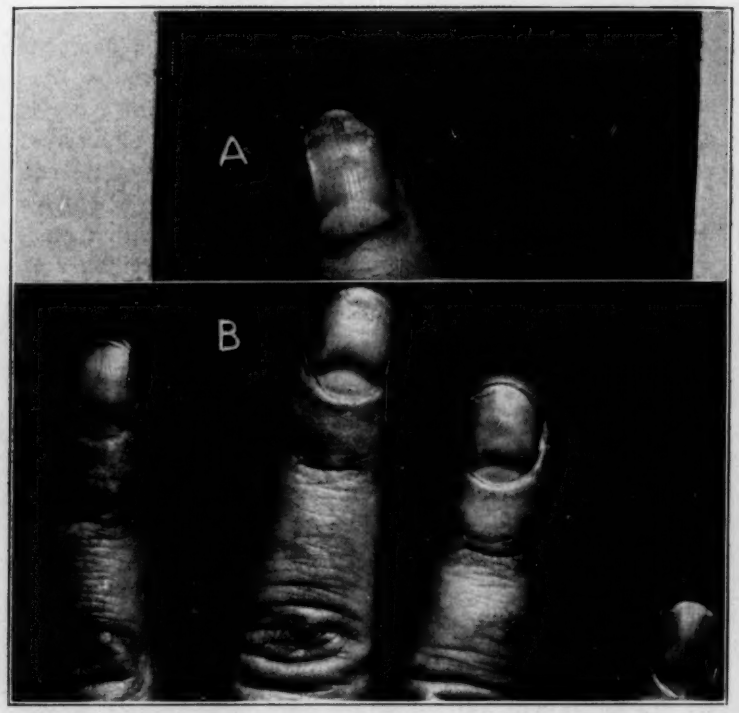

Fig. 1.—*A*, transverse furrow, parallel to the matrix already having traversed three fourths of the nail on the thumb of a diabetic person. The record shows poor control of diet twenty weeks prior. *B*, multiple waves toward the free edge of several fingers, most evident on the middle finger. The record shows that this patient was under poor control about fifteen weeks before for about a month. No new transverse furrows appeared during the sixteen weeks before this article was written, during which period the patient was under control.

Fig. 2.—The wavy appearance of multiple transverse furrows on the great and second toes is readily observed in the case of a diabetic person not under medical supervision.

be 0.1 mm. per day and that of the covered proximal portion of the nail 3 to 4 mm., one may expect to see a pathologic process appear from thirty to forty days after the metabolism of the matrix has been altered. In some cases, the distance between individual furrows corresponded to the interval of poor control of the diabetic process. This enabled us to judge the intensity and the duration of the metabolic disturbance. We have not encountered new furrows after the establishment of good carbohydrate balance. We have, however, observed multiple furrows when carbohydrate metabolism was not well controlled.

THEORY OF MECHANISM

All observers agree that a disturbance of nail production of the matrix causes furrows to appear. Some have stated the belief that this is due to a vasomotor component and that in fevers the nail bed presents a turgescence which compresses the nail against the nail wall, causing the nail to grow more rapidly and to be thinner. This theory, however, is not applicable to afebrile conditions. Other theories presume that there is an arrest of nail growth during fevers. Hutchinson [7] attributed the production of furrows to a disturbance of the peripheral circulation, thus causing a decreased rate of growth in the nails. Only Papillon [8] has studied the microscopic anatomy of transverse furrows. He maintained that in the formation of furrows merely the thickness of the nail is reduced; however, he did not investigate either the nail bed or the matrix.

COMMENT

None of the theories appear to us to explain this phenomenon adequately. Since we known the stratum germinativum to be the only germinating layer of nail growth, it would appear to us that any process that alters metabolism in this stratum might cause the production of transverse furrows. The nutrition of the stratum germinativum is diminished in direct ratio with the diminution of the nutrition of the organism. This process would explain the appearance of transverse furrows in the course of and following all the pathologic conditions enumerated.

Transverse furrows have frequently been observed in the nails of diabetic persons. These ridges may be used as helpful diagnostic criteria in evaluating the past nutritional and metabolic state.

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7. Hutchinson, J.: Cases Illustrating the Effects of Nerve Section on Nutrition and Animal Heat, M. Times & Gaz. **1**:328, 1863.

8. Papillon, A.: Des sillons des ongles chez des aliénés, Thesis, Lyon, no. 1141, 1896; cited by Heller,[4] p. 71.

HUMAN INFECTION WITH ECTHYMA CONTAGIOSUM, A VIRUS DISORDER OF SHEEP

REPORT OF TWO CASES

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Ecthyma contagiosum, known also as sore mouth and by other names, is a virus infection of sheep and related animals that is world-wide in its distribution. It affects chiefly the lambs and is characterized by herpetic and later ulcerative crusted lesions of the mouth and occasionally of other areas. Because of the loss of weight during an attack and less so because of the mortality, the disorder is of immense economic importance in sheep grazing countries. Vaccination of animals with an attenuated virus has been successful in controlling the infection. Infection of human beings with this virus has been reported from most countries. In the American literature there is only one report, by Schoch.[1]

A filtrable virus is the cause of ecthyma contagiosum, and Aynaud[2] was one of the first to work extensively with the disease. He proved it to be a virus disease transmissible only by inoculation to the mucous membrane and skin of material found in the dried crusts or seropurulent matter in the pustules of the natural infection. Intravenous or subcutaneous injection of the virus material does not produce the disease. The saliva and the blood serum do not contain the virus, and the serum of an animal that has recovered has no protective antibodies that will inactivate the virus when mixed with active infectious material, but an attack confers permanent immunity. The virus is resistant to drying and freezing and can be kept at room temperature for long periods, retaining its virulence. Aynaud showed that vaccination with dilutions of the virus, attenuated by drying and placing in glycerin and physiologic solution of sodium chloride, gave rise to a mild reaction which conferred

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From the Department of Dermatology and Syphilology, University Hospitals, State University of Iowa.

Read at the Sixty-Third Annual Meeting of the American Dermatological Association, Inc., Colorado Springs, Colo., June 1, 1940.

1. Schoch, A.: Sheep Pox Infection in Man, Arch. Dermat. & Syph. **39**:1040 (June) 1939.

2. Aynaud, M.: La stomatite pustuleuse contagieuse des ovins (chancre du mouton), Ann. Inst. Pasteur **37**:498 (May) 1923.

immunity. Boughton and Hardy [3] in extensive field trials demonstrated that the incidence of ecthyma contagiosum in lambs vaccinated by this method was 0.38 per cent and in the unvaccinated controls 65.3 per cent. Thus vaccination is of great economic importance in sheep-raising communities where ecthyma contagiosum is endemic. These investigators also showed that the virus will pass a Mandler N filter and remain infectious. They corroborated most of Glover's [4] work done earlier. They showed by cross immunity experiments that the virus is distinct from the vaccinia-variola group and also that the rabbit, guinea pig, calf and dog are immune to cutaneous inoculation and the rabbit to corneal inoculation. The goat is, however, susceptible to the virus and suffers from the disease; it is possible that wild animals of related species also have the disorder.

The natural infection in sheep comes shortly after the lambs are put on pasture in the spring. A few lambs become infected from the dried crusts on the range in which the virus from the previous season is still viable; within two weeks it becomes epidemic and affects most of the lambs. The infection is spread probably by contaminated water and forage and less by direct contagion.

The natural infection as seen in the United States is usually mild and occurs almost only in lambs and chiefly on the lips. Ewes which have not had the infection may have lesions on the udder acquired from a suckling lamb. A few lesions may be present on the nostrils and about the eyes, but lesions on the body are rare. Ulcerative lesions of the mouth, tongue and pharynx occasionally occur and may be serious. It is probable that the ulcerative lesions are caused by secondary infection with Actinomycosis necrophorus. In Texas secondary infestation of the oral lesions with blow fly larvae causes a great deal of trouble and is the chief cause of death in the lamb. The loss is chiefly in that the lambs lose much weight during activity of the disease and are retarded in growth. Sheep and lambs not previously infected or vaccinated may acquire the infection during the period they are in feeding lots on their way to market. The mortality is small and is caused by the complications.

After an incubation period of several days, the disease begins on the lamb's lips as one or several small papules, which within twenty-four hours become small, clear, fluid-filled, discrete vesicles. In another day the contents are seropurulent or purulent. Many new lesions appear at this time and during the next few days undergo the same change.

3. Boughton, I. B., and Hardy, W. T.: Contagious Ecthyma (Sore Mouth) of Sheep and Goats, J. Am. Vet. M. A. **85**:150 (Aug.) 1934.

4. Glover, R. E.: Contagious Pustular Dermatitis of Sheep, J. Comp. Path. & Therap. **41**:316 (Dec.) 1928.

The pustules rupture and leave an ulcerated surface which becomes covered with crusts made up of dried serum and leukocytes. The crusts are ⅛ inch (0.32 cm.) or more thick and are formed by coalescence of several pustules. Removal of the crusts leaves a red, raw, elevated, granulating surface. The lips are swollen, edematous and painful, so that the lamb cannot eat or suck and is uncomfortable. There are no fever or constitutional symptoms in the uncomplicated case, but there is great loss of weight. The infection lasts from fourteen to forty days, with an average of twenty-one or less.

A few cases of human infection have been reported briefly in the veterinary literature of foreign countries. Schoch recently reported the first case in the United States, that of a man with a single pustular local infection on his thumb. Hardy earlier reported his personal case after handling the virus material in his experiments. Peterkin [5] in England reported 5 cases in which the local infection went on to simulate granuloma pyogenicum. Oppermann and Stümpke [6] reported a case in which a local primary infection was followed by a generalized vesicular eruption. Though they did not recognize the condition, Robert and Orbaneja [7] reported 2 cases of granuloma-pyogenicum-like lesions of the face, probably ecthyma contagiosum, as they had handled a chamois that had sore mouth.

Gallivan,[8] director of a commercial laboratory in which animal vaccines and serums are produced, stated that many of his workers who help prepare the vaccine become inoculated and that minor pustular lesions develop on their hands when they first start to work. He stated the belief that the disease occurs in sheep ranchers but that they pay little attention to it. He stated that he had been informed of 2 cases in which the condition occurred in severe form in persons vaccinating sheep with the virus. The disease must be more common than reports indicate. Almost all the reported cases are instances of local inoculation, like the 2 to be reported.

REPORT OF CASES

The first patient had vaccinated sheep against sore mouth on Sept. 17, 1938 with a commercial vaccine. In the course of the vaccination he accidentally contaminated his hands with the virus. Four days later he noted swelling in several areas with

5. Peterkin, G. A. G.: The Occurrence in Humans of Contagious Pustular Dermatitis of Sheep ("Orf"), Brit. J. Dermat. **49**:492 (Nov.) 1937.

6. Oppermann, T., and Stümpke, G.: Der Lippengrind (Ekthyma contagiosum) der Schafe und seine Übertragbarkeit auf den Menschen, Arch. f. Dermat. u. Syph. **176**:337, 1937.

7. Robert, P., and Orbaneja, G.: Trois cas de granulomes angiopapillomateux éruptifs infectieux, Ann. de dermat. et syph. **8**:45 (Jan.) 1937.

8. Gallivan, F. M.: Personal communication to the author.

pain and redness. Shortly thereafter blisters appeared, which became filled with pus. After a few days the pustules ruptured in a few places, but the lesions progressed until he was seen, which was ten days after the inoculation.

He then had three lesions, one large one (fig. 1) on the first joint of the left thumb and two smaller ones on the third finger of the right hand and the second finger of the left hand. The lesion on the thumb was 3 by 2 cm., elevated, angry red and painful. There were three small crusts in the center of the lesion, which were surrounded by a pus-filled, tense, elongated bulla, and surrounding this was an inflammatory areola. The other lesions were the same, only smaller. There was no enlargement of the regional glands, no fever and no constitutional symptoms; a general physical examination showed no abnormalities. The Wassermann reaction of the blood was negative, and agglutination tests for tularemia, typhoid and malta fever gave negative results. The lesions healed without complications in three weeks.

Material from the large pustule was studied by Hale,[9] of the department of bacteriology, who has worked a great deal with filtrable viruses. There were only a few contaminating organisms on direct smear. The

Fig. 1 (case 1).—Lesion of ecthyma contagiosum of a purulent type ten days after onset.

material was inoculated into the cornea and skin of a rabbit and into mice and guinea pigs, but the experiments were without result. It was later learned that these animals usually used for the study of virus disease are naturally immune to the virus of ecthyma contagiosum. For this reason and because no susceptible animals were available, bacteriologic study was not carried out in the second case.

The second patient noted swelling of his thumb one week after he had wormed some lambs. In the course of a few days blisters appeared, which soon became purulent. They continued to progress until he was seen, two weeks after the onset. He presented three lesions, two small ones on the right forefinger and one large one on the thumb (fig. 2) at the base of and to the lateral side of the nail. The large lesion was over 3 cm. in its greatest dimension and consisted of a crusted center at the base of the nail, surrounded by a pustular zone, which was in turn surrounded by an inflammatory areola. Toward the lateral side of the nail there was also pus beneath the skin. The smaller lesions were about 1 cm. in

9. Hale, W. M.: Personal communication to the author.

diameter and had a central pustule and inflammatory halo. There was no regional adenopathy, and the results of a complete physical examination, agglutination tests and Wassermann tests were normal. No attempt was made to isolate the virus in this case.

The diagnosis of ecthyma contagiosum is not difficult, as the disease occurs in persons who handle infectious material, either the animals or the vaccine. The local condition closely resembles the ordinary vaccination take. The well developed pustule surrounded by an inflammatory areola is characteristic. Regional adenopathy is absent or mild, and there are no general symptoms. Tularemia has a slight resemblance, but the presence of a noncharacteristic primary inoculation site, enlarged regional glands and constitutional symptoms and a positive result of an agglutination test enable one to diagnose this disorder. Sporotrichosis, with its primary inoculation site and later development of subcutaneous lesions, is differentiated by the slow course and the successive development of subcutaneous gummas up the arm. Primary syphilis and tuberculous chancre may resemble slightly the lesion of infectious ecthyma but can be differentiated by local observations, laboratory tests and subsequent course. Pyogenic infections caused by the staphylococcus or the streptococcus could closely resemble ecthyma contagiosum and be difficult to exclude except by collateral evidence, such as exposure to the infection. All diseases which have a primary lesion at a site of inoculation must be considered in differential diagnosis.

Fig. 2 (case 2).—Lesion of ecthyma contagiosum two weeks after onset. The lesion was crusted and granulomatous in the center.

SUMMARY

Ecthyma contagiosum is a virus disease of sheep characterized by vesicular and, later, crusted lesions of the mouth. The virus can attack human beings exposed to it, giving rise to a highly inflammatory, purulent or crusted lesion at the points of inoculation. Two cases of local inoculation in men are reported.

ABSTRACT OF DISCUSSION

DR. LOUIS A. BRUNSTING, Rochester, Minn.: These patients present an unusual condition, and the diagnosis might easily have failed to be made if Dr. Nomland had not been aware of the possibilities of infection in this particular occupation. There is a similarity between ecthyma contagiosum and accidental vaccination against smallpox in human beings.

In the course of a recent public health program, including controlled vaccinations, I saw 3 persons who had atypical lesions but who had not been vaccinated directly. One patient was a woman who had a lesion on the chin, which was somewhat impetiginous, with enlargement of the cervical nodes and severe constitutional symptoms. She had never been vaccinated but had accidentally acquired the inoculation from her child. Another patient, a woman, was vaccinated accidentally on the arm as a result of contact of the skin with that of the vaccinated site of a child while she was riding with him in the seat of an automobile. The third patient was a child who was accidentally contaminated from other members of the family who had been vaccinated.

Atypical vaccinations against smallpox can be rather puzzling, especially if there are systemic reactions, and they have a course somewhat similar to that of the disease which Dr. Nomland has described.

DR. ARTHUR G. SCHOCH, Dallas, Texas: I naturally was extremely interested in the 2 cases that Dr. Nomland has reported. I should like to reemphasize one point and ask Dr. Nomland a question.

Since seeing an example of this condition, I have asked numerous sheep ranchers in Texas whether they were familiar with this condition in human beings. Most sheep ranchers or men who work with sheep are familiar with it and vaguely recall having received scratches or minor injuries and having had pustules develop at the site years previously. They seek no medical aid for the condition, for they consider it a rather trivial secondary infection and, I dare say, scarcely recognize the nature of the true infection. In other words, in the majority of cases, sheep handlers are inoculated with this virus. The disease goes through a definite course, rather mild, which apparently renders them immune to further infection.

One question I should like to ask Dr. Nomland: Did the lesion in the 2 patients resolve without scarring?

DR. RUBEN NOMLAND, Iowa City: Apparently the disease in most instances is of minor importance, and in the 2 cases I observed did not result in scarring. The lesion itself so closely resembles the take of a vaccination that it is not ordinarily difficult to diagnose.

Another fact that indicates that this condition occurs more frequently than is usually believed is the statement Dr. Tomlinson made to me this afternoon, that he had seen 2 patients, a physician and his wife, with lesions at the site of inoculation with virus of this disease after the handling of sheep that they had on their ranch.

EPIDERMOLYSIS BULLOSA: A CLINICAL AND BACTERIOLOGIC STUDY

REPORT OF FOUR CASES

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AND

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NEW YORK

This study of epidermolysis bullosa was undertaken when, in the course of making a routine clinical examination, we found that the patient, a 13 month old girl, had an abnormally high leukocyte count (10,200 per cubic millimeter). While looking for the cause of the leukocytosis we made a bacteriologic study of the bullous exudate from one of the lesions as well as of a smear of material from the throat, and to our surprise we obtained from both an almost pure culture of an unusual type of hemolytic streptococcus (group G, Lancefield).

The occurrence of Streptococcus haemolyticus in the bullous fluid of lesions of epidermolysis is in itself not uncommon. Marchionini,[1] among others, reported that he found an abundant growth of this organism, as well as of Staphylococcus aureus, in the lesions which he examined, and it has for the most part been considered only a secondary contaminant. But this, so far as we know, is the first time that this unusual strain of Str. haemolyticus has been isolated from, or at least identified in, a patient with this disease. More as a matter of curiosity than because we expected any positive results, we examined the bullous fluid of 3 other patients, who also proved to have a high leukocyte count as well as other evidences of infection, and found the same strain of hemolytic streptococcus in the lesions of two of them.

It seemed to us interesting to make an attempt to ascertain whether the presence of the group G type of Str. haemolyticus in these 4 patients might possibly be of some causal significance in their disease.

Read at the Sixty-Third Annual Meeting of the American Dermatological Association, Inc., Colorado Springs, Colo., May 31, 1940.

From the Department of Dermatology and the Department of Bacteriology, College of Physicians and Surgeons, Columbia University, and the Vanderbilt Clinic.

1. Marchionini, A.: Ueber Epidermolysis bullosa dystrophica vegetans: Beiträge zu einer klinischen Sonderform, zur Pathogenese und Prognose der kongenitalen Epidermolysis, Arch. f. Dermat. u. Syph. **176**:347, 1938.

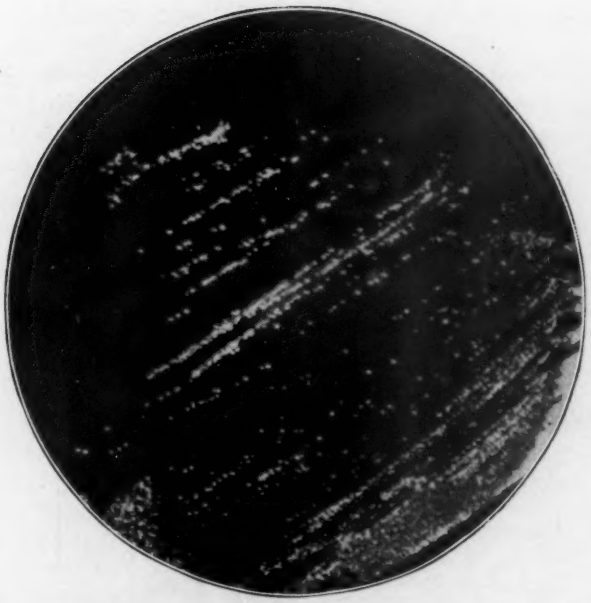

Fig. 1.—Str. haemolyticus (group G, Lancefield), from bullous fluid; twenty-four hour culture.

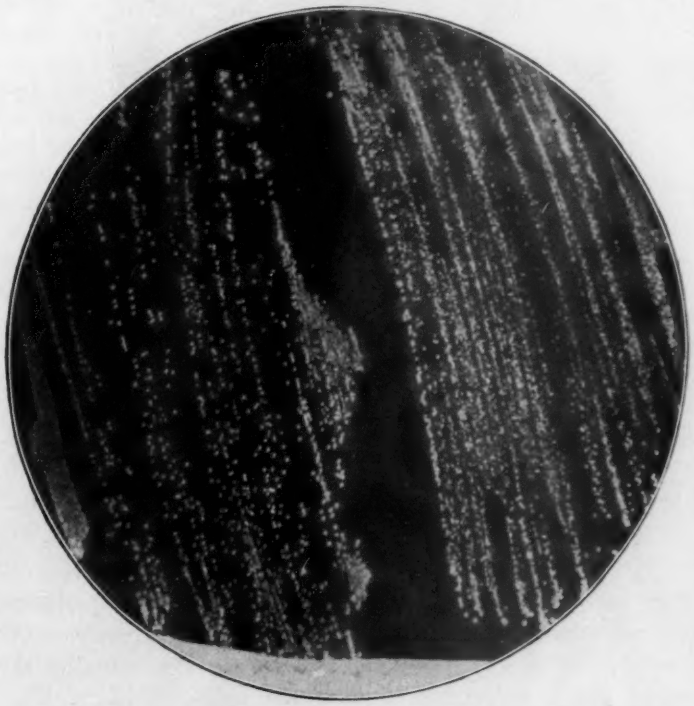

Fig. 2.—Str. haemolyticus (group G, Lancefield), from bullous fluid; forty-eight hour culture.

Nothing definite is known as to the cause of either of the two universally recognized forms of epidermolysis bullosa, the simple and the dystrophic form, or of another form, epidermolysis bullosa tarda ("acquisita"), which is sometimes included. The generally accepted opinion is that epidermolysis bullosa is a congenital anomaly of the skin, though concerning the nature of this anomaly there is no great agreement except for one more or less constant feature, namely, a diminution

Fig. 3.—Epidermolysis bullosa, showing the distribution of the lesions.

in the amount of elastic tissue. The one known etiologic factor common to all forms is heredity. Others which have been accused are: metabolic and endocrine disorders, instability of the vasomotor supply of the blood vessels, autointoxication, trophic nervous disorders and infection.

Since our experiments are as yet by no means complete, we can make no definite statements at this point as to a causal connection between the group G strain of Str. haemolyticus and epidermolysis bullosa. But the evidence which we have found thus far, and which we present here, suggests the existence of such a relation.

The material forming the basis of this report was derived from the study of 4 patients with epidermolysis bullosa, of whom 2 were boys 17 and 3 years old respectively and 2 were females, 29 years and 13 months old, respectively. All were of Russian Jewish birth or extraction. Three of them had the simple form of the disease, while the fourth, the 17 year old boy, had the dystrophic form. Two of them, the 29 year old woman and the 13 month old child, were mother and daughter. The others were completely unrelated, both familially and geographically.

Complete clinical and bacteriologic tests were made in all of these cases.

REPORT OF CASES

CASE 1.—C. P., a white girl aged 13 months, had a recurring bullous eruption involving principally the face, neck and extremities. Blisters had been noted on the wrists and ankles shortly after birth and had persisted with more or less severity ever since, recurring usually at the sites of earlier lesions. Even the slightest pressure or friction produced bullae. The patient had no subjective symptoms except intermittent and moderately severe itching, which appeared after the bullae had ruptured. The mother suffered with the same disease. Otherwise the family and past histories were irrelevant.

The patient's general physical condition was good. She could not crawl, pull herself up to a standing position, stand alone or talk. Physical examination gave essentially negative results.

Examination of the skin revealed numerous generalized vesicular and bullous eruptions, most evident on the extensor surfaces and varying in size from that of a pea to that of a dime. Some of the lesions contained a clear fluid, while in others the fluid was decidedly cloudy. Some eroded, bleeding and crusted pea-sized to dime-sized areas were visible. Other sites of former lesions which had healed were macular, red and somewhat atrophic.

A summary of the details of the clinical tests made on this patient, as well as on the 3 other patients, will be given in a separate section.

CASE 2.—R. P., a Russian Jewish housewife aged 29, had been married four years and had one child 13 months old (case 1). There had been no other pregnancies.

When first seen this patient complained of a severe recurrent bullous eruption which had been present since two weeks after birth. The past and family histories were irrelevant except for the fact that a niece of the patient's father was said to have had similar eruptions.

The patient had never been free from lesions since the onset of the disease. The bullae always appeared at sites of pressure or injury, developing on apparently normal skin and being found principally on the dorsa of the hands and fingers, the feet, the ankles, the elbows and wherever the clothing fitted tightly. At first they contained a clear fluid, which changed later to a thick yellow puslike material. The bullae ruptured, discharged and became crusted. Sometimes blood appeared in the blisters, and painful sores remained after the vesicles ruptured. The lesions apparently bore no relation to pregnancy or menstruation, but they were much worse in warm weather. There were no other constitutional symptoms.

General physical and neurologic examination gave essentially negative results.

The backs of the hands and fingers, the elbows, the knees, the ankles and the dorsa of the feet were covered by a moderate number of pea-sized to dime-sized bullous lesions. The fluid in some of these bullae was clear; in others, cloudy. A few red scars appeared on the dorsa of the hands and feet.

CASE 3.—I. L., a white boy aged 17 years, was first admitted to the Vanderbilt Clinic seven years ago, on account of a recurrent generalized bullous eruption and a thick, irregular, hornlike condition of the nails. The dystrophy of the nails had existed since birth. No bullae were seen until the patient was about 2 years old, but after that time they were almost constantly present, appearing at the sites of injury or pressure, chiefly on the elbows, knees, backs of the fingers, hands, dorsa of the toes, feet and ankles, as well as on the shoulders, buttocks and thigh. For the last year or two, however, the lesions had been limited mainly to the heels and feet. The bullae never entirely disappeared, although there were periods when the skin was much freer than at other times. The blisters ruptured, leaving raw, crusted areas, many of which contained pus. The nails were removed several times, mainly for cosmetic reasons. Occasionally bullae appeared under the nails, which became infected and were shed. The soles and palms were greatly thickened, and there were follicular keratotic lesions on the extensor surfaces of the extremities and of the body. Sores also appeared in the nostrils, followed by bleeding. The bullae ruptured, leaving bleeding, raw, pruritic surfaces. Sometimes the lesions on the feet were so painful that the patient was unable to walk.

The past, family and personal histories were irrelevant.

General physical and neurologic examination gave essentially negative results.

Examination of the skin disclosed a few bullae on the dorsa of the feet and the sides of the heels, some containing a clear and others a cloudy fluid, besides some large, eroded, crusting and oozing areas on the sides and backs of the heels and between and on the dorsa of the toes. These parts were extremely tender. The nails were in various stages of development. Many had already been removed surgically. There was a low grade paronychia, with redness, swelling and tenderness, around some of the nails.

CASE 4.—M. L., a white boy aged 3 years, was admitted to the Vanderbilt Clinic complaining of vomiting spells and a generalized bullous eruption. The patient was born at full term by normal delivery and seemed entirely well at birth. When the attending physician swabbed out the infant's mouth the mucous membrane rubbed off and blisters appeared. Within twenty-four hours the child's entire body was covered with blisters. He has never been entirely free from them since except on one day, when he had a temperature of 106.2 F. due to a gastrointestinal disturbance.

The lesions usually began as small red blotches, followed in a few minutes or a few hours by bullae. They cleared up eventually, leaving no scars. The patient had frequent vomiting spells, especially when he became excited or when blisters appeared in his mouth.

The skin bruised easily, and blisters formed at the sites of injury. The patient did not begin to walk until he was 3 years old. He had received orange juice, irradiated ergosterol (viosterol in oil) and dicalcium phosphate daily since birth.

The family history was irrelevant.

Physical examination showed him to be poorly developed and poorly nourished but otherwise normal and healthy.

There was a general eruption on the skin, consisting of bullae and erythematous macular areas at sites from which other bullae had disappeared previously. The

lesions were most numerous on the extensor surfaces of the extremities, the neck and the folds of the body. Most of the bullae contained a serosanguineous fluid, but others had clear or cloudy contents. Some of the bullae had ruptured, the raw surfaces which remained being covered by heavy grayish yellow crusts. Other denuded areas were red, and a clear serous material oozed from them.

CLINICAL REPORT

Results of chemical examination of the blood, which included tests for non-protein nitrogen, sugar, calcium, phosphorus, phosphatase, albumin, globulin, total protein and serum bilirubin, were all within normal limits, except for the phosphatase. Three of the patients showed a high blood phosphatase content (case 1, 9.55 Bodansky units; case 3, 4 [high normal], and case 4, 10).

A total of 19 blood counts was made in the 4 cases. The noteworthy feature was the strikingly high leukocyte count. With the exception of one count each for the 2 adults (6,100 per cubic millimeter in case 2 and 8,000 in case 3) all 4 patients had leukocytosis, the counts varying from 10,200 to 20,000 per cubic millimeter. The hemoglobin content varied from 61 to 109 per cent in these nineteen readings. There was no eosinophilia. The erythrocyte sedimentation rate was entirely normal.

The arsenic content of the blood was normal except in case 2, in which it was 0.2 mg. per hundred grams of whole dry blood.

The cell count in the bullous exudate was normal, except for the eosinophils (in case 1 there was an eosinophil count of 9; in case 2, of 13).

The urine was normal in all cases except case 1, in which on two occasions there was a slight albumin content (trace to 1 plus) and, microscopically, white blood cells of from 2 to 10 per high power field.

The arsenic content of the urine was normal.

No coproporphyrin was found in the urine.

The basal metabolic rates were all within normal limits (— 10 to + 7 per cent).

The electrocardiograms were all normal.

Roentgenograms of the skull, long bones, thymus, gallbladder, gastrointestinal tract, and chest were normal for all 4 patients, except for a healed tuberculous lesion in the chest of the patient in case 2.

Cultures of the blood, examinations of the stool and Wassermann and Kline tests all gave negative results.

The antistreptolysin titer was normal for all patients.

The Dick test gave a positive result in cases 1 and 2 (the patient in case 1 was an infant 13 months old) and a negative result in cases 3 and 4.

All 4 patients were tested with staphylotoxin, streptotoxin, old tuberculin and monilia toxin. The only positive results were a positive reaction to old tuberculin in cases 2 and 3.

The special neurologic examinations and psychometric tests gave results within normal limits for all patients.

The histologic changes were in the main consistent with those usually observed in cases of epidermolysis bullosa, particularly in regard to the increased vascularity, the infiltration of the corium and the presence of edema. Under orcein staining the elastic tissue of the papillary layer was seen to be greatly decreased, but that of the reticularis was normal in amount.

BACTERIOLOGIC REPORT

Bacteriologic specimens obtained from the 4 patients were streaked on blood agar plates and inoculated into tubes of nutrient and anaerobic broth.

Case 1.—On two different occasions the contents of four bullae ranging in age from one to four days were examined. A heavy growth of hemolytic streptococci was obtained from 3 of the 4 specimens. One specimen, twenty-four hours old, yielded an apparently pure culture of hemolytic streptococcus. A hemolytic streptococcus was also obtained from a smear of the patient's throat. After twenty-four hours, four or five colonies were visible on the blood plate. Specimens from the tears, vagina, feces and several areas of the normal skin revealed no hemolytic streptococci.

Staphylococcus albus was also present, the number apparently varying in direct proportion to the age of the lesion.

The hemolytic streptococci obtained from the bullae and the throat, when tested against specific rabbit antiserums by Lancefield's [2] method, were all found to belong to group G (Lancefield).[2a]

The patient's serum was tested against known extracts obtained from Dr. Lancefield and against an extract of the hemolytic streptococcus obtained from the patient in case 3. A positive precipitin reaction was obtained with both extracts.

The Dick test gave a positive result.

The same procedure was followed in cases 2, 3 and 4.

Case 2.—In this case the lesions were much less numerous than in case 1, and the bullae were more infrequent.

The contents of six bullae one to four days old were obtained on three different occasions. Five of these six specimens yielded hemolytic streptococci. One bulla, of twenty-four hours' duration, was sterile. The bullous fluid varied from clear, straw-colored fluid to blood-tinged serum to frank pus.

Specimens from the skin near the lesions and from an area free from lesions, as well as from the nose, throat, vagina, feces and conjunctiva, showed no hemolytic streptococci.

All cultures of hemolytic streptococci obtained from the bullae were typed in the same manner as for the patient in case 1, and found to belong to group G.

The precipitin test (Lancefield) was performed with this patient's serum against the same extracts as those used with the serum of the patient in case 1. No positive reaction was obtained.

The Dick test gave a positive result.

Case 3.—Five of 5 specimens of bullous fluid yielded a hemolytic streptococcus. Two of these specimens were pustules. A pure culture of Str. haemolyticus (group G) was obtained from them.

Specimens from the skin of the face and legs—the latter being the site of the majority of the lesions in this patient—yielded one and two colonies, respectively,

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2. Lancefield, R. C.: Microprecipitin Technic for Classifying Hemolytic Streptococci, and Improved Methods for Producing Antisera, Proc. Soc. Exper. Biol. & Med. **38**:473, 1938.

2a. It should be mentioned here that all of the cultures of material taken from these patients, after being typed by us, were given to Dr. Rebecca C. Lancefield, of the Rockefeller Institute for Medical Research, for typing. Dr. Lancefield found them to be such an antigenically pure strain of group G that she now uses them as the stock strain for that group.

of Str. haemolyticus. No such organisms were found in the nose, throat or feces of this patient. All of the hemolytic streptococci isolated belonged to group G (Lancefield).

The Dick test gave a negative result.

Case 4.—Specimens were taken on two occasions from blisters at various sites and cultured as in the 3 cases just reported. No organisms were obtained from any of the specimens.

The Dick test gave a negative result.

ANALYSIS OF BACTERIOLOGIC DATA

The strains of the hemolytic streptococcus isolated in cases 1, 2 and 3 showed a moderate pathogenicity in animals. Three of 6 mice inoculated intraperitoneally with 0.1 cc. of undiluted broth culture of the strain of Str. haemolyticus obtained from these patients died within twenty-four hours. Pure cultures of group G streptococci (Lancefield) were recovered from the peritoneal cavities, heart blood and brains of these mice. Group G antibodies (precipitins) were found in the serum of the patients in cases 1 and 3, but none were demonstrable in that of the patient in case 2 (mother of the patient in case 1).

In our clinical examination we had found indubitable signs of the presence of infection. The first of these was the abnormally high leukocyte count in all 4 patients (it ranged from 10,200 to 20,000 per cubic millimeter, only two of nineteen readings being within normal limits [case 2, 6,100; case 3, 8,000]). The constant exacerbations and remissions of the disease also pointed to an infective source, as did the inflammatory reaction in the tissue.

Our bacteriologic studies seemed to point to the group G strain of Str. haemolyticus isolated from the lesions of 3 of our patients as a possible cause of this infection, the evidence being (1) the heavy growth of this strain in the lesions of 3 of the patients, to the virtual exclusion of any other organism; (2) the positive precipitin reaction of the serum of the patient in case 1 against streptococci from the patients in cases 2 and 3, and (3) the high sensitivity of 2 of the patients (cases 1 and 2) to the Dick test. (The reaction of the patient in case 1 to the Dick test is of particular interest for our thesis, since she was only 13 months old.)

In view of the many brilliant successes recently attained in the treatment of streptococcic infections with sulfanilamide, we decided to try the effect of that drug on our patients.

SULFANILAMIDE THERAPY

The bacteriostatic action of sulfanilamide on in vitro cultures of standard strains of Str. haemolyticus is already a well established fact, but its effect is not so well known in respect to group G. Long and Bliss [3]

3. Long, P. H., and Bliss, E. A.: The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, The Macmillan Company, 1939, p. 120.

said that the group G strain is sensitive to sulfanilamide, but they did not state whether this sensitivity is an in vivo or an in vitro one. We therefore tried to determine that fact by making in vitro tests with sulfanilamide. We found the group G strain isolated in cases 1, 2 and 3 to be extremely sensitive to sulfanilamide. It was decided then to see what effect, if any, would be produced in vivo by the administration of therapeutic doses of sulfanilamide both by mouth and by topical application over the affected areas. A 1 per cent solution was used for topical application. Standard doses were given orally to the 2 adults (cases 2 and 3), but for the children (cases 1 and 4) the dosage was calculated according to age and weight.

Only 1 of the 4 patients (the boy in case 3, the only patient with the dystrophic condition in the group studied) has received consistent treatment, both orally and topically. His condition has shown a decided improvement. Many of the bullae have completely disappeared, and others have healed without scarring. His general physical condition as well has noticeably improved. He states emphatically that he is better now than he has ever been.

The other 3 patients have received only sporadic treatment with sulfanilamide; hence no definite conclusions can be drawn from their condition. It is interesting to observe, however, that in cases 1 and 2 not a single organism has been obtained from any lesion since the initiation of sulfanilamide therapy. The patient in case 4, of whom it has already been remarked that the lesions were sterile from the very beginning of our investigation, had been given sulfanilamide therapy at another institution after isolation of Str. haemolyticus, group B, from the lesions, before he came to the Vanderbilt Clinic. This fact may or may not have vitiated our results.

COMMENT

The presence of hemolytic streptococci in the bullous fluid of patients with epidermolysis bullosa has been established by previous investigators (Marchionini [1] and others). Most of them, as we said before, have regarded the organism merely as a secondary contaminant. It is true, of course, that streptococci are found on the normal skin. Thomson and Thomson [4] cited the figures of various investigators, among them Frederic (1901) and Haxthausen (1927), both of whom found streptococci occurring in the normal skin of 7.5 per cent of the patients studied. We examined the skin of 69 different persons picked at random from the patients in the department of dermatology of the Vanderbilt Clinic and presenting 28 different cutaneous diseases. The lesions, most of which

4. Thomson, D., and Thomson, R.: Historical Survey of Researches on Rôle of Streptococci in Skin Diseases, Ann. Pickett-Thomson Research Lab. 7:111 (July) 1931.

were of the vesicular type, were tested bacteriologically. The contents of the vesicles varied from clear fluid to frank pus. Staph. albus, Staph. aureus and occasionally Streptococcus viridans were obtained. In no case, however, was Str. haemolyticus demonstrated. Almost 50 per cent of the specimens were sterile. It would seem, therefore, that Str. haemolyticus does not function as a secondary contaminant in cutaneous lesions nearly as often as most dermatologists have heretofore assumed.

One cannot, of course, state categorically that in those cases in which Str. haemolyticus is found on the human skin it must necessarily act in the role either of a secondary contaminant or of a primary causative agent. It is evident, however, from Colebrook and Purdie's [5] study of 106 cases of puerperal sepsis, in 4 of which they isolated the group G strain of Str. haemolyticus, that this particular strain is capable of acting as a pathogen. Lancefield [6] also expressed this opinion.

In our 4 cases none of the patients except those in cases 1 and 2 had any connection with each other, either familially or geographically. The abundant growth of the group G strain of Str. haemolyticus in the lesions of 3 of the patients before any treatment was instituted, its complete absence from the lesions in cases 1, 2 and 3 after administration of sulfanilamide and particularly the definite improvement of all symptoms in case 3 under consistent treatment with sulfanilamide seem to us to indicate the probable incrimination of Str. haemolyticus (group G, Lancefield) as a contributory infectious factor in the causation of epidermolysis bullosa.

SUMMARY AND CONCLUSIONS

A clinical and bacteriologic study is presented of 4 cases of epidermolysis bullosa, 3 of the simple and 1 of the dystrophic type.

Str. haemolyticus (group G, Lancefield) was isolated from the bullous lesions of 3 patients and from a smear of material from the throat of 1 of the 3. The fourth patient, in whom all lesions were sterile, had received sulfanilamide before this study was begun.

In vitro tests showed that the organism possessed a decided sensitivity to sulfanilamide. Consistent administration of the drug to 1 patient by oral and topical application resulted in healing of the bullous lesions and definite improvement of the patient's general condition. In 2 other patients, who received less consistent treatment with sulfanilamide, the lesions became completely sterile. The clinical symptoms, however, were not greatly affected.

It is suggested, in view of these results, that infection with Str. haemolyticus (group G) may be of some significance in the causation of epidermolysis bullosa.

5. Colebrook, L., and Purdie, A. W.: Treatment of One Hundred and Six Cases of Puerperal Fever by Sulfanilamide, Lancet **2**:1237 (Nov. 27) 1937.

6. Lancefield, R. C.: Personal communication to one of us (M. S.).

ABSTRACT OF DISCUSSION

DR. RICHARD S. WEISS, St. Louis: I should like to ask the authors whether they made any biopsy studies of material from the apparently normal skin of these persons.

As most dermatologists will remember, years ago Engman and Mook reported a series of cases in which the elastic tissue was diminished, fragmented or, in some areas, almost entirely gone. These studies were confirmed by Kanoky and Sutton, and I reported a case in which the same elastic tissue deficiency was found.

Many cultures have been made of material from the bullae of epidermolysis bullosa, and various organisms have been grown, but I have never been able to attribute any etiologic significance to the organisms isolated. I did not find a streptococcus of that particular variety, as I recall it. I am inclined to believe that in the cases observed by Dr. Cannon and his associates the lesions were perhaps contaminated, as he mentioned; that they were made more severe by the secondary infection, and that they improved when sulfanilamide was administered. I should like to know what their present status is and whether they still show the criteria necessary for a diagnosis of epidermolysis bullosa. Do they present Nikolsky's sign, for instance? Do bullae develop at present after trauma? If they do not, and if these were cases of true epidermolysis bullosa, this perhaps is a significant contribution.

DR. H. J. TEMPLETON, Oakland, Calif.: About a year ago one of the obstetricians of Oakland picked up a newborn baby by its heels with one hand and swabbed out its mouth with the other to resuscitate it. The mucous membrane of the lips all came off, and the epidermis slid off from the ankles down. The history disclosed that a paternal uncle had died shortly after birth with the same disease. A diagnosis of epidermolysis bullosa congenita was made.

Cultures of material from some of the blebs were made later, but no streptococci were obtained, all the cultures being sterile. One positive result, such as that obtained by Dr. Cannon and his associates, is worth a hundred negative ones.

In the case of the infant just mentioned, in spite of the fact that it was known that developmental defect was present, injection of chorionic gonadotropin (antuitrin S), injection of whole blood and administration of snake venom were tried, to no avail. The only treatment which helped was spraying the denuded areas with gentian violet as one does in treating a burn, putting on occlusive dressings and not disturbing those dressings for two or three weeks and suspending the child's legs and buttocks from an overhead frame, such as orthopedists use in treating a fracture of the hip. Removal of trauma is probably what produced healing. The child has lived and has gone home from the hospital. New blisters still appear, however, on trauma.

DR. RUBEN NOMLAND, Iowa City: I wish to discuss what Dr. Weiss brought up regarding the elastic tissue changes associated with epidermolysis bullosa. I had the good fortune to study at autopsy an infant similar to the one Dr. Templeton described. As far as could be determined, there was no disturbance of the elastic tissue, which seemed completely normal both in the unaffected skin and in the blistered area.

I also studied 1 other case, the patient being a young adult who showed no abnormal elastic tissue changes where no blisters had been present. On the other hand, where there had been numerous blisters and some dystrophic changes in the skin, there was a disturbance of the elastic tissue.

DR. A. BENSON CANNON, New York: I am sorry if I have given the impression that we thought we had found a cause and a cure for epidermolysis bullosa. I presented the results of our study here with the hope of receiving constructive criticism of the work already done, together with suggestions for further investigation of the subject.

As was stated in the paper, we thought that isolation of a pure strain of Str. haemolyticus (group G, Lancefield) from the lesions of 3 of our 4 patients was sufficiently unusual and interesting in itself to warrant a more extensive study of the cases, an opinion in which we were supported by Dr. Lancefield, of the Rockefeller Institute, who herself first isolated the strain of hemolytic streptococcus which we found in our patients.

There was definite clinical evidence of infection—the abnormally high leukocyte count in all 4 cases, the strong inflammatory reaction in the tissue and the constant exacerbations and remissions of the disease. The fact that a streptococcus of the group G strain was practically the only micro-organism isolated from any of the lesions and that it occurred in remarkably heavy growth forced us to consider the possible significance of this infectious agent. When we found that 2 of the patients (1 of them a child) had a positive Dick reaction and that a positive precipitin reaction was obtained with the serum of 1 patient when it was tested against extracts of the hemolytic streptococci obtained from another patient; and when we considered the fact, established by Colebrook and Purdie and confirmed by Dr. Lancefield, that the group G strain of Str. haemolyticus is capable of acting as a pathogen, we felt still more strongly that there must be, in these cases at least, some relation between this strain and epidermolysis bullosa.

We took biopsy specimens only from the lesions; none were taken from the normal skin. In every specimen the pathologic changes were consistent with those of epidermolysis bullosa, the tissue showing increased vascularity, infiltration of the corium, decided edema and almost complete absence of elastic tissue.

As for treatment, we do not by any means claim to have found a cure for epidermolysis bullosa in sulfanilamide. But we do say that in the 1 case in which consistent and adequate treatment with that drug was given many of the lesions have disappeared completely, and the rest have healed without scarring. The patient's general physical condition, too, has improved noticeably. The other 3 patients, who did not adhere closely to the plan of treatment, have shown occasional improvement, with some remissions. We feel that we shall have to observe all of these patients for a much longer period than we have yet done before we can evaluate properly the significance, if any, of sulfanilamide in the treatment of this condition.

EXPERIMENTAL AND CLINICAL OBSERVATIONS WITH HISTAMINASE

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AND
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About ten years ago Best and McHenry discovered that certain organs of the dog, particularly the gastrointestinal tract and the kidney, contained a substance capable of inactivating histamine.[1] To this material they attributed the characteristics of an enzyme, and they suggested the name histaminase. They found that it could be prepared in the form of a stable powder so that chemical and physical properties were more readily studied. These investigators found that certain optimum conditions were essential for the maximum activity of histaminase, namely, incubation with the substrate for twenty-four hours at 37 C. and a hydrogen ion concentration of 7.2. Under these conditions detectable destruction of histamine occurred only after an incubation period of four hours. Best and McHenry also defined a convenient unit of histaminase as the amount necessary to destroy 1 mg. of histamine under the aforementioned optimum conditions.

Using a commercial preparation,[2] Felix[3] was unable to alter the effect of histamine on the guinea pig uterus, the blood pressure of cats and rabbits and the bronchial volume of cats. To a great extent he confirmed the observations of Best and McHenry pertaining to the physical conditions necessary for inactivation. He showed, further, that the expected gastric response to histamine in human beings is unaltered

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From the Institute of Pathology and the Department of Dermatology, Western Pennsylvania Hospital.

Read at the Sixty-Third Annual Meeting of the American Dermatological Association, Inc., Colorado Springs, Colo., June 1, 1940.

1. Best, C. H.: The Disappearance of Histamine from Autolyzing Lung Tissue, J. Physiol. **67**:256 (June) 1929. Best, C. H., and McHenry, E. W.: The Inactivation of Histamine, ibid. **70**:349 (Dec.) 1930.

2. The preparation used was torantil (or T. 360), manufactured by the Winthrop Chemical Co., Inc., New York, and supplied in ampules of 1 and 2 units as well as in tablets of 5 units, a unit being as defined in the text.

3. Felix, I.: Experimental and Clinical Investigations of the Action of Histaminase Contained in Extracts of the Mucous Membrane of the Intestines on Histamine, Acta med. Scandinav. **95**:1, 1938.

by either oral or intramuscular administration of the histaminase preparation. This was in confirmation of the reports of Biguria and Canzanelli [4] as well as those of Atkinson and Ivy [5] on dogs. Bosse,[6] in this laboratory, was unable to demonstrate any effect on the Shwartzman phenomenon in rabbits by pretreatment with histaminase administered orally, intravenously or subcutaneously. This work was undertaken because of the known increase in histamine content of the tissues at the site of the reaction.

From all these observations it appears that the originally postulated incubation period of Best and McHenry is probably vital to histamine-histaminase neutralization.

However, contradictory results have been obtained by other investigators. Thus MacGregor and Peat,[7] using a kidney-lung preparation perfused with defibrinated blood, showed that if ten times the histamine content of the lung is added to the blood the greater part of the added histamine was inactivated within five minutes, although the natural histamine of the lung remained intact. Suzuki [8] contended that histaminase in the pretreated animal detoxifies histamine rapidly, basing his opinion on the behavior of gastric secretions in animals pretreated with histaminase and then given injections of histamine. Such rapidity of action is in harmony with the opinion of Takebayashi,[9] Ungar and Bolgert [10] inhibited the development of pulmonary lesions resulting from inhalation of hydrochloric acid vapors in guinea pigs by injection of 2 units of histaminase three minutes before the inhalation. The experiments of Karady and Browne [11] appear to be the most thought provoking, and

4. Biguria, F., and Canzanelli, A.: The Effect of Continued Oral Administration of Histaminase and Pancreatin on Gastric Secretion, Am. J. Physiol. **110**: 243 (Nov.) 1934.

5. Atkinson, A. J., and Ivy, A. C.: The Action of Histaminase on the Gastric Secretory Response to Histamine and to a Meal, Am. J. Physiol. **107**:168 (Jan.) 1934.

6. Bosse, M. D.: The Effect of Histaminase on the Shwartzman Phenomenon, J. Lab. & Clin. Med., to be published.

7. MacGregor, R. G., and Peat, S.: The Histamine-Histaminase System in the Isolated Perfused Kidney-Lung Preparation, J. Physiol. **77**:310 (Feb.) 1933.

8. Suzuki, R.: Studien über den experimentellen Nachweiss der das Histamine im lebendigen Körper vernichtenden Histaminasenwirkung, Taiwan Igakkai Zassi **47**:68 (Jan.) 1937.

9. Takebayashi, R.: Die Bedeutung des Histamins in der experimentellen Pathologie und Chirurgie, Deutsche Ztschr. f. Chir. **249**:256, 1937.

10. Ungar, G., and Bolgert, M.: Essais de prevention des lésions pulmonaires mortelles consécutives à l'inhalation de vapeurs irritantes par l'acide ascorbique et par l'histaminase, Compt. rend. Soc. de biol. **129**:1107, 1938.

11. Karady, S., and Browne, J. S. L.: Effect of Histaminase Treatment on Histamine and Anaphylactic Shock in Guinea Pigs, J. Immunol. **37**:463 (Nov.) 1939.

the results reported seem to justify the use of histaminase in cases of clinical allergy. They were able to protect all of 20 guinea pigs from anaphylactic symptoms and death by intrajugular injection (with the animals under mild ether narcosis) of 3 units of histaminase fifteen minutes before administration of a shocking dose of egg white. In a control group of 10 animals, severe signs of anaphylaxis were obtained in all, and 4 of the animals died after ten to fourteen minutes.

EXPERIMENTAL DATA

This particular phase of the histaminase problem has interested this laboratory for the past eight months. Various methods were employed in a series of experiments [12] designed to allow an adequate incubation period for the histamine-histaminase interaction; the results failed to demonstrate any protective action of histaminase in the anaphylactic syndrome of guinea pigs. Therefore it appeared advisable to apply the technic of Karady and Browne to another series of animals, in which only a fifteen minute incubation period for the histamine-histaminase interaction was allowed.

METHOD

Sixty-nine guinea pigs averaging 200 to 300 Gm. in weight were sensitized by subcutaneous injection of 3 cc. of filtered 50 per cent egg white. On the fifteenth and sixteenth days after sensitization, 32 animals received an intrajugular injection of 3 units of histaminase.[13] To accomplish this it was not necessary to anesthetize the animals. Fifteen minutes later the animals received an intra-abdominal shocking dose of 2 cc. of filtered 50 per cent egg white. On a similar schedule, 32 control animals received the shocking dose. A second group of controls, consisting of 5 sensitized animals, was given the intravenous injection of histaminase alone.

All animals were carefully observed, and the time of appearance of symptoms was recorded at frequent intervals for one hour. Observations were then made each hour for four hours and at the eighteenth and twenty-fourth hours.

RESULTS

The results are enumerated in table 1. In the control group of 32 animals, the average interval before onset of the first symptom was eight minutes and the average interval before death was thirty-nine minutes. Death occurred in 20 animals, or 62.5 per cent. All animals showed the classic symptoms of anaphylaxis.

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12. Knoll, A. F.: The Ineffectiveness of Pretreatment with Histaminase on Anaphylactic Shock in Guinea Pigs, to be published.

13. The histaminase employed throughout this study was that prepared by the Winthrop Chemical Co., Inc., of New York, and sold under the name torantil. Some of the material was donated by this concern.

In the group of 32 animals pretreated with histaminase, the average interval before onset of the first symptom was ten and three tenths minutes and the average time of interval before death was thirty-six minutes. Death occurred in 19 animals, or 59.4 per cent. One animal failed to show any symptoms.

The rapidity of onset or the severity of symptoms was not proportional to the period of survival. Autopsy was performed on the animals which died, and all exhibited the classic asphyxial distention of the lungs. No death could be attributed to trauma of injection. The 5 sensitized animals which received intravenous injections of histaminase alone were symptom free.

TABLE 1.—*Comparison of Anaphylactic Phenomena in Guinea Pigs Pretreated with Histaminase and in Guinea Pigs Not Pretreated*

	Controls	Histaminase *
Number of guinea pigs	32	32
Earliest onset of symptoms	2 minutes	3 minutes
Latest onset of symptoms	20 minutes	31 minutes †
Average onset of symptoms	3 minutes	10 minutes
Earliest time of death	5 minutes	9 minutes
Latest time of death	173 minutes	91 minutes
Average time of death	39 minutes	36 minutes
Number of deaths	20	19
Mortality percentage	62.5	59.4
Autopsy	Asphyxial distention	Asphyxial distention

* Histaminase (3 units dissolved in 2 cc. of solution, freshly prepared) was injected into the jugular vein 15 minutes prior to intra-abdominal injection of the shocking dose of egg white.
† One animal showed no symptoms.

In addition to the animal experiments the following procedure was carried out in human beings. Twenty-five laboratory workers and assistants without a history of allergy were given intracutaneous injections of histamine phosphate (1:1,000) sufficient to raise the epidermis in a wheal with a diameter of 2 to 3 mm. The mean diameter of the wheal and of the erythema was noted at five, ten and fifteen minute intervals. At a later date these subjects were given 85 units of histaminase by mouth, with an initial dose of 25 units and 15 units each hour thereafter for four hours. One-half hour after the last dose they were given intracutaneous injections of histamine as before. There was no appreciable diminution in the size of the wheal or of the area of associated erythema.

From the clinical series reported here, 25 patients were chosen at random for intracutaneous injections before and at the conclusion of therapy. The minimum total dose of histaminase in this group was 600 units, and the maximum total dose was 1,680 units. There was no

significant change in the characteristics of the wheal after conclusion of histaminase treatment as compared with those observed prior to treatment. These observations in human beings are in accordance with those of Rostenberg and Sulzberger.[14]

COMMENT

It seems evident that the clearcut negative results obtained in a series of animals larger than any previously reported on [11] do not support the claims of a rapid in vivo action which apparently rationalized certain of the clinical applications of histaminase. Negative results in other experiments,[12] in which a longer period for the histamine-histaminase interaction was allowed, would seem to support Dale,[15] who maintained that there is no justification for assuming that histamine is the only harmful cell constituent liberated by injury and that consequently one need not expect so specific a substance as histaminase to alter strikingly the anaphylactic reaction. However, the weight of the experimental evidence obtained by other investigators seems to favor the original concept of Best and McHenry in regard to the destruction of histamine by histaminase. Perhaps the contradictory results obtained can be attributed to variations in the stability or potency of the product used. If this is the case, one would expect that clinical applications of histaminase would give parallel results.

ANALYSIS OF CLINICAL REPORTS

Clinical trial of histaminase preparations, aside from favorable experimental results, appeared to be indicated by the work of Albus,[16] who incubated a like amount of histamine with a given quantity of blood from a normal person and with the same amount of blood from an allergic person. The results suggested a diminished histaminase content of the blood in the allergic person. A somewhat similar suggestion was made by Goodson.[17] The widespread use of histaminase and the interest its clinical application has aroused in the treatment of the various allergic diseases has prompted this report of experiences with this form of therapy.

There are in the literature at present about 25 clinical reports on the effect of histaminase on various allergic conditions and also on unrelated

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14. Rostenberg, A., and Sulzberger, M. B., in discussion on Laymon and Cummings.[18b]

15. Dale, H. H.: Croonian Lectures on Some Chemical Factors in the Control of the Circulation, Lancet **1**:1285 (June 22) 1929.

16. Albus, G.: Ueber die Aktivität der Histaminase und der Cholinesterase beim latenten Allergiker, Klin. Wchnschr. **18**:858 (June 17) 1939.

17. Goodson, W. H., Jr.: Physical Allergy, Proc. Staff Meet., Mayo Clin. **13**: 500 (Aug. 10) 1938.

dermatologic lesions. The reports which give specific information [18] are cited in table 2. It is seen that although a total of 254 patients have been treated with histaminase and 58 per cent have been considered decidedly improved, the individual reports, except for several recent publications, are concerned with small series varying from 1 to 5 cases. Furthermore, the impression is gained that most of the reports, particularly in foreign journals, reflect an unjustifiable overenthusiasm.

In addition to the reports cited in table 2, there are others, which are difficult to evaluate. Roth and Rynearson [19] used histaminase with variable results in 12 cases of allergic manifestations caused by insulin. Abel, Siebert and Earp,[20] assuming that chilling predisposes to the development of fibrositis, used histaminase "with encouraging results"

18. (*a*) Forman, J.: The Use of Histaminase in the Treatment of Various Allergic Manifestations, Ohio State M. J. **36**:56 (Jan.) 1940. (*b*) Laymon, C. W., and Cummings, H.: Histaminase in the Treatment of Urticaria, and Atopic Dermatitis: Preliminary Report, J. Invest. Dermat. **2**:301 (Dec.) 1939. (*c*) Miller, H., and Piness, G.: Histaminase in Treatment of Allergy, J. A. M. A **114**:1742 (May 4) 1940. (*d*) Ertl, E.: Zur endonasalen Heufieberbehandlung, Monatschr. f. Ohrenh. **71**:122 (Jan.) 1937. (*e*) Ertl, E.: Zur Therapie des Heuschnupfens, Wien. klin. Wchnschr. **52**:643 (July 7) 1939. (*f*) Matras, A., in discussion on Urbach.[18q] (*g*) Rothman, S., in discussion on Laymon and Cummings.[18b] (*h*) Foshay, L., and Hagebusch, O. E.: Histaminase in Treatment of Serum Sickness, J. A. M. A. **112**:2398 (June 10) 1939; (*i*) Serum Sickness: Effective Treatment and Probably Prophylaxis by Means of Histaminase, ibid. **112**:1102 (March 18) 1939. (*j*) von Hartmann, M.: Ueber die Behandlung der Akne vulgaris mit Torantil, Dermat. Wchnschr. **106**:693 (June 18) 1938. (*k*) Doucas, C.: Zwei Fälle von polymorpher Akne vulgaris behandelt mit Torantil, ibid. **108**:713 (June 24) 1939. (*l*) Adelsberger, L.: Darmextrakte bei allergischen Krankheiten, Fortschr. d. Therap. **13**:568 (Oct.) 1937. (*m*) Roth, G. M., and Horton, B. T.: Hypersensitiveness to Cold: Treatment with Histamine and Histaminase, Proc. Staff Meet., Mayo Clin. **14**:353 (June 7) 1938. (*n*) Baker, T. W.: Histaminase in Treatment of Cold Allergy, J. A. M. A. **114**:1059 (March 23) 1940. (*o*) Vaisberg, M.: Histaminase in Treatment of Physical (Heat) Allergy and Some Other Conditions, New York State J. Med. **39**:2199 (Dec. 1) 1939. (*p*) Doucas, C.: Lupus erythematodes behandelt mit Torantil, Dermat. Wchnschr. **109**:812 (July 8) 1939. (*q*) Urbach, E.: Intestinal-toxisch bedingter Charakter einer chronisch rezidivierender Purpura durch Torantil festgestellt, Zentralbl. f. Haut- u. Geschlechtskr. **54**:70, 1936. (*r*) Prickman, L. E., in discussion on Foshay and Hagebusch.[18i] (*s*) Eustis, A.: The Relation of Histaminase to Toxemia and Asthma, New Orleans M. & S. J. **92**:350 (Jan.) 1940.

19. Roth, G. M., and Rynearson, E. H.: The Use of Histamine and Histaminase in the Treatment of Allergic Reactions to Insulin, Proc. Staff Meet., Mayo Clin. **14**:353 (June 7) 1938.

20. Abel, O., Jr.; Siebert, W. J., and Earp, R.: Fibrositis, J. Missouri M. A. **36**:435 (Nov.) 1939.

TABLE 2.—*Tabulation of Clinical Results Obtained by Various Authors with Histaminase*

Manifestation	Total Number of Cases	Pronounced Improvement: Number of Cases Reported by Different Observers	Pronounced Improvement: Total Number	Pronounced Improvement: Per Cent of All Cases	Slight Improvement: Number of Cases Reported by Different Observers	Slight Improvement: Total Number	Slight Improvement: Per Cent of All Cases	No Improvement: Number of Cases Reported by Different Observers	No Improvement: Total Number	No Improvement: Per Cent of All Cases
Urticaria	63	10 [18a]; 10 [18c]; 7 [18b]	27	43	2 [18b]	2	3	1 [18a]; 5 [18b]; 5 [18g]; 1 [18f]; 22 [18e]	34	54
Serum sickness	39	1 [18a]; 20 [18h]; 13 [18i]	34	87	.....	..	..	2 [18h]; 3 [18i]	5	13
Allergic rhinitis	35	1 [18a]; 5 [18i]; 9 [19]	15	43	1 [18i]; 4 [19]	5	15	2 [18i]; 13 [19]	15	42
Hay fever	34	2 [18a]; 5 [18d]; 12 [18e]	19	56	1 [18a]; 9 [18e]	10	29	3 [18c]; 2 [18e]	5	15
Acne vulgaris	27	25 [18j]; 2 [18k]	27	100	.....	..	..	.....	..	..
Allergic dermatitis	5	.....	..	..	.....	..	..	5 [18c]	5	100
Asthma	13	1 [18a]; 4 [18s]	5	38	2 [18a]	2	15	1 [18a]; 5 [18c]	6	47
Atopic dermatitis	11	3 [18a]	3	27	.....	..	..	8 [18b]	8	73
Physical allergy	5	1 [18m]; 2 [18n]; 2 [18o]	5	100	.....	..	..	.....	..	..
Angioneurotic edema	3	1 [18i]; 2 [18a]	3	100	.....	..	..	.....	..	..
Migraine	2	1 [18a]	1	50	.....	..	..	1 [18a]	1	50
Pruritus	2	2 [18a]	2	100	.....	..	..	.....	..	..
Purpura	1	1 [18q]	1	100	.....	..	..	.....	..	..
Lupus erythematosus	1	1 [18p]	1	100	.....	..	..	.....	..	..
Contact dermatitis	1	.....	..	..	.....	..	..	1 [18a]	1	..
Totals	242	.....	143	59	.....	19	8	.....	80	33

for patients showing sensitivity to cold. Moldenschardt [21] considered histaminase valuable in cases of seborrheic eczema, pyoderma, contact dermatitis, angioneurotic edema and serum sickness, although the number of cases was not mentioned. Decided improvement was reported by Ercklentz and Ercklentz [22] in cases of gastritis, peptic ulcer, hepatic cirrhosis and colitis.

AUTHORS' CLINICAL OBSERVATIONS

A total of 134 patients were treated with histaminase. The drug was given orally in every case. In 120 of the cases no other therapy, local or otherwise, was given, and in the remaining 14 cases no change was made in the local therapy in use at the time histaminase was instituted.

In the group with acute urticaria, the 13 patients were taken as they presented themselves. Six of these had received no previous treatment, and the remaining 7 had failed to respond to other therapy. There were 5 patients who obtained complete relief, and 3 of these had had no other therapy. Three patients who had responded to primary therapy suffered recurrences, which were not relieved by readministration, so that their cases were relegated to the unimproved group.

The patients who appeared to benefit most from the treatment with histaminase were those with atopic dermatitis. These were chosen because of the failure of other recognized forms of therapy. The duration of the disease in this group averaged three years. Ten of the 21 patients showed pronounced improvement within ten to fourteen days, although recurrences were evident when medication was suspended. One patient received a daily dose of 20 units, with continued relief over a nine month period. Ten patients showed no improvement, and in 1 case slight relief from pruritus was noted.

Fourteen patients with allergic or contact dermatitis, each of whom gave a positive reaction to a patch test with the irritant suspected, were given histaminase therapy. Four were clinically cured; 1 was slightly improved, and 9 obtained no relief.

Two patients with hay fever and asthmatic sequelae were given pronounced relief. Of 7 patients with bronchial asthma, moderate improvement occurred in 2, while 5 were resistant to treatment.

Four patients with serum sickness were treated, and striking results were obtained within eighteen to seventy-two hours in 3 cases. In 1 the condition failed to be alleviated.

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21. Moldenschardt, H.: Torantil, ein aus Darmschleimhaut gewonnes Präparat, Med. Klin. **32**:153 (Jan. 31) 1936.

22. Ercklentz, W., and Ercklentz, B. W.: Ueber Anti-Histaminwirkung im Organismus durch "Torantil," München. med. Wchnschr. **83**:17 (Jan. 3) 1936.

Two patients with conditions diagnosed as erythema multiforme were clinically cured within ten days; 1 obtained slight relief, and 3 absolute failures were noted.

Seven patients with allergic rhinitis were treated, but only 1 showed pronounced improvement. Three were somewhat relieved, and the remaining 3 were symptomatically unchanged, although histaminase was administered for three to nine weeks, with daily doses averaging 40 units.

A total of 29 patients with acne vulgaris were treated with an average daily dose of more than 50 units (40 units daily for two weeks and 60

TABLE 3.—*Clinical Effect of Histaminase*

Diagnosis	Total Number	Pronounced Improvement	Slight Improvement	No Improvement
Allergic				
Acute urticaria	13	5	0	8
Chronic urticaria	13	0	0	13
Physical urticaria	3	1	2	0
Atopic dermatitis	21	10	1	10
Angioneurotic edema	3	1	0	2
Contact (allergic) dermatitis	14	4	1	9
Erythema multiforme	6	2	1	3
Asthma and hay fever	12	2	2	8
Serum sickness	4	3	0	1
Allergic gastroenteritis	1	1	0	0
Migraine	4	1	1	2
Allergic rhinitis	7	1	3	3
Total	101	31	11	59
Nonallergic (miscellaneous)				
Acne vulgaris	29	3	3	23
Senile pruritus	2	1	0	1
Pruritus ani	2	0	0	2
Total	33	4	3	26
Grand total	134	35	14	85

A total of 134 patients were treated with histaminase. The drug was given orally in every case. In 120 of the cases no other therapy, local or otherwise, was given, and in the remaining 14 cases no change was made in the local therapy in use at the time histaminase was instituted.

units daily for four weeks). Three of these showed pronounced improvement; 3 showed slight improvement, and 19 were unaffected. Local applications and dietary corrections were excluded from the therapeutic regimen. These results are considerably different from those presented by von Hartmann [18j] and Doucas,[18k] who observed astonishing results in 27 cases in which the patients were treated by the injection method. No dosage was mentioned, but it was probably lower than the dosage used in our series.

A miscellaneous group consisting of 4 patients with migraine, 2 with pruritus ani, 2 with senile pruritus and 1 with allergic gastroenteritis were also treated. The patients with pruritus ani failed to improve. In 1 case of senile pruritus of three years' duration there was complete

amelioration of symptoms two weeks after administration of histaminase was started, and there were no recurrences at least four months later with a daily maintenance dose of 20 units. In this particular case the value for nonprotein nitrogen in the blood was 52 mg. per hundred cubic centimeters. In the other case of senile pruritus the content of the blood was normal; the patient secured no relief. One patient with migraine of four years' duration, with monthly attacks, had only one attack in the four months during which histaminase was administered. The other 3 patients were not benefited.

No serious side effects were encountered that could be attributed to histaminase. A few minor reactions were observed, such as nausea, which occurred on four occasions, and dizziness, which occurred twice. Single instances of constipation, diarrhea, headache, vomiting and blurred vision were recorded. The average dose used was 40 units daily, and the maximum dose, 105 units daily. One patient was treated for nine months, and another patient received a total of 10,620 units.

The results obtained with histaminase in a series of 134 cases of various conditions on a possible allergic basis were not very encouraging. Only 26.1 per cent of the patients showed decided improvement, and an analysis of this group reveals that almost half the number (15) had either atopic dermatitis or acute urticaria. The very nature of these 2 entities, which includes spontaneous regression or complete involution, makes interpretation of results difficult. Thus Rackemann [23] stated that great caution must be utilized for accurate determination of the value of any therapy for these diseases.

SUMMARY AND CONCLUSIONS

The syndrome of anaphylaxis in guinea pigs is unaffected by pretreatment with histaminase.

Intracutaneous wheals produced by histamine in normal, as well as allergic, persons are not altered by oral pretreatment with histaminase.

Of 101 patients suffering from diseases on an allergic basis and 33 patients suffering from miscellaneous disturbances treated with histaminase, pronounced improvement was obtained in only 35, or 26.1 per cent. The unimproved group was subject to therapy for six weeks, with an average daily dose of 50 units. More than one half of the patients who were decidedly improved were afflicted with atopic dermatitis or acute urticaria, two diseases given to spontaneous regression and even complete involution. Interpretation of the improvement noted in these cases is, therefore, difficult.

The results with acne vulgaris were practically negative.

The toxic effects from histaminase were negligible.

23. Rackemann, F. M.: Allergic Diseases with Special Reference to Histamine and Acetylcholine, New England J. Med. **222**:674 (April 18) 1940.

ABSTRACT OF DISCUSSION

Dr. William Harvey Guy, Pittsburgh: If dermatologists have had the same experience as general practitioners have had in the use of histaminase, they will agree that there was occasion for a study such as Drs. Knoll and Beinhauer have made. Every physician in the county medical society is using the drug as a cure-all for practically all dermatologic conditions, and it is apparent that somebody knows a great many things that are not so.

One hears glowing reports of complete cure of atopic dermatosis and the like. It was with these facts in mind that Drs. Knoll and Beinhauer started their study. In the clinical application they had some difficulty because of the fact that in going through the clinic rooms I would find half a dozen patients who were receiving histaminase for the treatment of acne and who were steadily getting worse and complaining about the treatment. I would feel sorry and would remove them from the authors' list, so that the large group of cases which they had intended to study was materially reduced in the long run.

To quote Dr. O'Leary, "When you believe, you stop thinking."

If dermatologists believe all the recommendation they have heard for administration of this drug in the control not only of physical allergy but of atopic dermatitis of all types, acne and a wide range of other conditions, they will reach a point where they will find nothing to do in dermatologic practice except hand out a few pills.

The end results are somewhat surprising in that there were some instances in which there was an apparent clinical response to the drug. I am inclined to believe that this was not actually the case, but I have gained the impression that histaminase may occasionally be of service in cases of physical allergy.

Dr. Francis W. Lynch, St. Paul: I hope that it may not be out of place to mention some studies relating to histamine rather than histaminase. Many dermatologists are familiar with the work of Code, who demonstrated that histamine, which is present in large amounts in the blood, is found chiefly in the eosinophils.

In more recent, and as yet unpublished, work, Code has shown that increased histamine in the esosinophils is associated with leukemia and pulmonary allergy but not with dermatologic allergy. Even though the eosinophilia may be great, there is little or no increase in the histamine content of the eosinophils. Thus there may be some fundamental difference between the histamine relations of dermatologic allergy and other types of allergy.

Dr. Louis A. Brunsting, Rochester, Minn.: Drs. Knoll and Beinhauer have made an excellent presentation. They have contradicted the previous evidence, which tended to show that anaphylaxis in animals could be interrupted by administration of histaminase. The value of histaminase for allergic diseases in human beings is subject to various interpretations, according to the enthusiasm of the observer. The observations of Foshay on the benefit of histaminase in the prevention of serum sickness are of particular interest. I have given the drug a thorough trial in cases of atopic dermatitis, and uniformly the benefits have been nil. There are a few conditions in which the use of histaminase has seemed to be of help, particularly chronic urticaria and angioneurotic edema. I can recall several instances in which the course of the disease was interrupted by this treatment after the disease had been established for one to two years. This may have been influenced in some instances by a natural tendency, based on wishful thinking, to see favorable results.

Before new drugs are introduced which are primarily of dermatologic interest or which have to do with the treatment of syphilis, it is advisable to have the results of carefully controlled observations presented in open meetings to such bodies as this association.

Dr. Carl W. Laymon, Minneapolis: The theory that various allergic reactions are due to the release of histamine following contact of the antigen with antibodies is an attractive one but, unfortunately, one which cannot be verified, as Drs. Knoll and Beinhauer have brought out.

Since 1937, at the University of Minnesota and the Minneapolis General Hospital, histaminase has been administered to patients with various dermatoses. To date there is a total of 56 cases. The results are much the same as those observed by Drs. Knoll and Beinhauer. In 11 cases of atopic dermatitis, as in Dr. Brunsting's cases, there was no improvement. In 7 cases of acne there was no noticeable change. In 1 case of dermatitis due to light there seemed to be partial relief. Two patients with dermographism had no benefit from histaminase.

The only cases in which there was benefit were those of urticaria. We tried to select patients with urticaria which had proved refractory to the various commonly used types of treatment before administering histaminase. In this group, which was composed of 35 patients, there seemed to be favorable results in about 60 per cent. However, in many of these cases a proper follow-up has been impossible; hence it is not known just what the subsequent course of the disease has been.

Dr. Marion B. Sulzberger, New York: All dermatologists are indebted to Drs. Knoll and Beinhauer for this work and for this presentation. It is, at best, an ungrateful task to check up on therapeutic agents of this kind. If one finds them effective it is nothing new, and if one is obliged to give negative reports on their efficacy one may make enemies and usually makes no friends. But I think it is a necessary type of work and is of great practical value.

Perhaps I may be permitted to say something about histaminase because I have had more or less experience with it for a number of years. It was used for many years in Europe before it was introduced in this country. I saw it used both in Zurich, Switzerland, and in Breslau, Germany, and have used it since sporadically and with uniformly negative results clinically.

I think that one interesting sidelight is that this work with histaminase has again brought up the question of the role of histamine in the production of allergic reactions. The results with histaminase would suggest that histamine is not the intermediate, universal wheal-producing substance in allergic reactions. I have always held that the entire theory of a universal common denominator or intermediate substance responsible for all allergic reactions or even for all urticarial reactions is untenable. As one of the many arguments against the universal role of histamine, I should like to point out a simple and interesting experiment which seems to me to suggest strongly that whealing, such as is seen in urticaria, is not actually produced by release of histamine in the tissues.

When one injects histamine into oneself or into an experimental subject intracutaneously in adequate doses to produce large wheals, one gets the most beautiful, prompt, classic urticarial reactions, not distinguishable in appearance from the reactions observed in cases of classic clinical urticaria or from those produced by introduction of allergens by intracutaneous injections or by scratch tests in specifically, actively or passively, allergic sites.

However, there is one decided difference. The wheals of urticaria and the wheals which one produces with allergens almost always itch, some of them

intensely. In my experience, the histamine wheals never itch. There is a sharp, stinging pain but no pruritus. This simple experiment seems to me to indicate that there is some radical difference between these two forms of wheal.

To return to the practical question, I think that in a summary of my own experience with histaminase given in every kind of dose, possibly up to as high as 60 tablets daily, and given by injection as well as by mouth (in Europe, there was an injectable product available), I can say that the controlled results were uniformly negative in every series of allergic or presumably allergic conditions in which I tried the medicament.

Dr. Lawrence G. Beinhauer, Pittsburgh: In answer to Dr. Brunsting, our assumption that histamine is a factor in the production of anaphylaxis is merely a repetition of the cold facts presented by Karady and Browne.

The unit used by Karady and Browne was used in this series. In another series of experiments, on over 100 animals, the type of substance used to produce the sensitization and a variable dosage for experimental work again gave negative results.

In the cases of atopic dermatitis that we reported, as I stated, we had no clinical cures, and evaluation of the results was difficult. We did not forget the classic work of Foshay, which I did not mention because of time but which is cited in the paper.

Again, I wish to call attention to the end results which we achieved. In our series of 134 cases we had 35 in which clinical improvement was noted, or 26.1 per cent, whereas in the existing literature on 258 cases a grand total of 58 per cent improvement was reported.

EFFECTS OF NEOARSPHENAMINE AND MAPHARSEN ON FORMED ELEMENTS OF BLOOD

GRANULOCYTOPENIA FOLLOWING NEOARSPHENAMINE THERAPY IN A PATIENT WHO SUBSEQUENTLY RECEIVED MAPHARSEN WITHOUT UNTOWARD REACTION

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Blood dyscrasias following administration of the arsphenamines have always been regarded with considerable concern. The development of such a reaction to arsphenamine therapy is an absolute contraindication to its further use, as well as to use of other members of the arsphenamine group.

McCarthy and Wilson,[1] in an excellent discussion of this subject, divided these dyscrasias into three groups: namely, thrombopenic purpura, granulocytopenia and aplastic anemia. While the majority of these reactions conform to one of these classifications, there are occasional reactions to these drugs which affect the blood and do not fall into any of these classes.

The purposes of this paper are:

1. To compare briefly the effects of neoarsphenamine and mapharsen on the formed elements of the blood of patients undergoing treatment for syphilis. The complete data on these investigations will be published in a separate report.

2. To report in detail a case of granulocytopenia following administration of neoarsphenamine. The patient later tolerated mapharsen without untoward reaction.

SUMMARY OF INVESTIGATIONS PREVIOUSLY REPORTED BY US

Our interest in the problem of the blood dyscrasias followig arsphenamine therapy was stimulated by the introduction of mapharsen for clinical trial in 1934. During a study of the therapeutic effects of this

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Read at the Sixty-Third Annual Meeting of the American Dermatological Association, Inc., Colorado Springs, Colo., June 1, 1940.

1. McCarthy, F. P., and Wilson, R.: The Blood Dyscrasias Following the Arsphenamines, J. A. M. A. **99**:1557 (Nov. 5) 1932.

drug, observations were made concerning its action on the formed elements of the peripheral blood in patients under treatment for syphilis. These observations were directed toward the following objectives: to note the effects of neoarsphenamine and mapharsen on the formed elements of the blood in patients with syphilis who had evidenced no untoward reactions to their administration; to note the effects of mapharsen on patients who had previously had a blood dyscrasia following administration of any of the arsphenamines; to clarify, if possible, our knowledge concerning the mechanism of these reactions, and to determine the influence of vitamin C in large amounts on the sensitivity of patients in whom thrombopenic purpura developed after administration of neoarsphenamine and bismarsen.

In previous reports [2] we have presented the data on 8 patients with thrombopenic purpura following administration of arsphenamine therapy. In 5 of these patients the reaction had been produced by neoarsphenamine and in 3 by bismarsen. It was determined that the thrombopenic purpura could be reproduced by administration of a very small amount of the offending arsphenamine or of a related member of the group. The reaction was sharp and at times simulated the nitritoid crisis. Symptoms of shock usually appeared promptly after administration of the drug. The effects on the peripheral blood were uniform, there being a rapid drop in the platelet count, which sometimes fell from 300,000 to 30,000 within an hour after the drug had been given. The other elements of the blood were little disturbed. Increased capillary fragility usually accompanied development of the purpura. Hemorrhage from the mucous membranes of the mouth and petechiae of the skin appeared promptly. Recovery occurred in each instance within a few days without any special form of treatment. The platelet count returned to normal in from four days to one week. Reproduction of the reaction definitely increased the patient's sensitivity to the offending drug, so that after the second experimentally produced attack the sensitivity was acute. This sensitization decreased in varying degrees in individual patients after arsphenamine therapy had been discontinued for several months, although complete desensitization did not occur.

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2. Falconer, E. H.; Epstein, N. N., and Wever, G. K.: Purpura Haemorrhagica Following the Administration of Neoarsphenamine: The Reaction to Neoarsphenamine Compared to the Reaction to Mapharsen, Arch. Int. Med. **58**:495-511 (Sept.) 1936. Falconer, E. H.; Epstein, N. N., and Mills, E. S.: Thrombocytopenic Purpura Hemorrhagica Due to the Arsphenamines: Sensitivity in Patients as Influenced by Vitamin C Therapy, ibid. **66**:319-338 (Aug.) 1940. Falconer, E. H., and Epstein, N. N.: Thrombocytopenic Purpura Hemorrhagica Following Neoarsphenamine and Bismarsen Therapy: Further Studies on Sensitivity to Arsphenamine and Tolerance to Mapharsen, ibid. **65**:1158-1177 (June) 1940.

In 7 of these patients with thrombopenic purpura to whom mapharsen was given later, no diminution of the platelet level occurred. One patient disappeared from observation before mapharsen could be used to test his sensitivity to this preparation.

Vitamin C in large amounts in the diet and in crystalline form was given orally and parenterally to 6 of the patients in this group known to be sensitive to the arsphenamines. The symptoms of thrombopenic purpura were neither prevented nor diminished by this procedure. In fact, it seemed as though the severity of the reaction was considerably increased, but this was undoubtedly due to the fact that each experimentally produced attack rendered the patient increasingly sensitive to the arsenical used.

Thrombopenic purpura following arsphenamine therapy is apparently due to a diminution of the platelets plus some toxic action on the vasomotor center controlling capillary tonus.

COMPARISON OF THE EFFECTS OF NEOARSPHENAMINE AND THOSE OF MAPHARSEN ON THE FORMED ELEMENTS OF THE PERIPHERAL BLOOD

Sixty patients with syphilis were selected for a study of the effects of neoarsphenamine and mapharsen on the formed elements of the blood; 30 were given neoarsphenamine and 30 mapharsen. These patients had not received treatment previously with either neoarsphenamine or mapharsen. All were followed in the hematologic clinic, blood counts being made just before each treatment and at fifteen, thirty, sixty and one hundred and twenty minutes after treatment. Our observations were made over periods varying from twenty-four hours to six months. Patients being watched for possible changes in the blood cells received bismuth preparations between the courses of neoarsphenamine or mapharsen. These studies indicated that no significant change occurred in the hemoglobin or the red blood cells of the average patient receiving either arsenical. There was a depression of the white cells and platelet counts in patients under treatment with neoarsphenamine. The white cells were not significantly affected by mapharsen, but the platelets after the first week of treatment tended to fall in some instances. No constant immediate drop in the platelet count at fifteen, thirty, sixty and one hundred and twenty minutes occurred with neoarsphenamine. Such a drop was reported by Mu [3] in 1929, and since then Mu's results have been frequently cited in the literature.

Certain changes have been observed in the lymphocyte-monocyte ratio. The implication of these changes is not apparent at present. Our

3. Mu, J. W.: Effects of Neoarsphenamine on the Number of Blood Platelets, Proc. Soc. Exper. Biol. & Med. **26**:407 (March) 1929.

data, which will present the details of monocyte-lymphocyte changes, are being prepared for publication. Certain discrepancies appeared in our original data after use of mapharsen, and a new series of cases at present is being observed with blood studies after administration of this drug. For this reason our conclusions concerning mapharsen can be stated only in a general way. It should be mentioned at this point that mapharsen apparently has serious potentialities for injuring the bone marrow, as 1 of our patients had so-called aplastic anemia after five doses of mapharsen. She had well marked anemia before we gave her mapharsen, and undoubtedly her bone marrow was vulnerable.

In general, our data tend to agree with the observations of Rosahn and Pearce [4] in regard to the effects of the arsphenamines on the formed elements of the blood.

GRANULOCYTOPENIA FOLLOWING NEOARSPHENAMINE THERAPY: REPORT OF CASE

M. L., a white man aged 35 years, entered the Mount Zion Hospital on Dec. 26, 1939, complaining of prostration, fever and sore gums and mouth. He stated that he had consulted his physician one month previously because of a generalized eruption. A strongly positive Wassermann reaction was obtained, and a diagnosis of secondary syphilis was made. He received an injection of bismuth subsalicylate at that time and three days later 0.3 Gm. of neoarsphenamine, without untoward reaction. Three days later he received another injection of the bismuth compound, followed in three days by a third and by one of neoarsphenamine (0.3 Gm.). The day after this last injection of neoarsphenamine the patient had a chill and felt ill and flushed. The next day he saw his physician and was ordered to bed because of a high fever. He remained in bed twelve days; his temperature, at first 104 F. (40 C.), gradually fell to normal. At this time he was given another injection of neoarsphenamine (0.45 Gm.) and again became ill and prostrated, the temperature rising to 105 F. (40.5 C.) about one and a half hours after the injection. After about one week of fever a blood count was taken, and because of a decided granulocytopenia he was referred to Dr. LeRoy Briggs, who sent him to the Mount Zion Hospital.[5]

Physical Examination.—He was prostrated and in considerable discomfort because of severe stomatitis. The gums were swollen, diffusely reddened and superficially ulcerated in areas. The rest of the buccal mucosa was similarly affected, although to a less degree. There was a general eruption on the trunk and limbs. This consisted of large discrete papules, many of which had disappeared, leaving a deep brownish pigmentation. There was moderate general adenopathy. No evidence of a healing primary sore was found. The liver and the spleen were not enlarged, and physical examination otherwise gave essentially negative results.

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4. Rosahn, P. D., and Pearce, L.: The Blood Cytology in Untreated and Treated Syphilis, Am. J. M. Sc. **187**:88 (Jan.) 1934.

5. One of us (N. N. E.) was called in by Dr. Briggs to care for the patient. The hematologic investigations were done in the hematologic clinic of the University of California under the direction of Dr. E. H. Falconer.

Laboratory Examinations.—The blood counts are given in table 1.

Examination of the urine on entry (December 26) showed a very slight trace of albumin; the sediment contained 50 to 60 white blood cells and 40 to 50 red blood cells per high dry field. Two casts were seen in the preparation. These urinary abnormalities cleared before the patient's discharge from the hospital.

The Wassermann and Kahn reactions of the blood were 4 plus.

Course in Hospital.—The patient's temperature remained between 38.8 C. (102 F.) and 39.4 C. (103 F.) for eight days and then began to fall, reaching normal on the eleventh day. The stomatitis improved as the febrile reaction subsided, and by the time the patient left the hospital, twenty-eight days after entry, he felt well except for some persistent general weakness. Table 2 shows the blood picture.

TABLE 1.—*Blood Counts in a Case of Granulocytopenia Following Neoarsphenamine*

Date	Hemoglobin Per Cent	Hemoglobin Gm.	Red Blood Cells per Cu. Mm.	Platelets	White Blood Cells per Cu. Mm.	Polymorphonuclears	Filamented Ratio	Nonfilamented Ratio	Eosinophils	Basophils	Monocytes	Lymphocytes	Metamyelocytes
12/26/39	81	12.5	4,250,000	.....	7,100	8	5	3	11	..	23	58	..
12/27/39	..	....	.....	360,000	6,350	4	..	4	9	..	32	55	..
12/29/39	..	....	.....	.....	5,950	0	..	..	18	2	35	45	..
12/30/39	..	....	.....	.....	5,950	2	..	2	..	5	50	43	..
12/31/39	..	....	.....	.....	7,350	0	..	..	..	..	50	50	..
1/ 2/40	76	11.7	4,130,000	.....	7,150	12	5	7	5	..	42	41	..
1/ 3/40	..	....	.....	.....	9,200	24	12	12	7	..	35	34	..
1/ 4/40	..	....	.....	.....	.....	20	3	17	6	..	36	35	3
1/ 5/40	..	....	.....	.....	18,750	25	4	21	3	1	37	30	4
1/ 8/40	74	11.4	3,980,000	.....	15,500	31	6	25	8	..	28	31	2
1/ 9/40	..	....	.....	.....	15,500	46	26	20	3	..	9	38	4
1/13/40	81	12.5	4,300,000	.....	11,450	50	30	20	3	..	10	34	3
1/14/40	..	....	.....	.....	18,850	54	35	19	5	..	7	33	1
1/16/40	..	....	.....	.....	7,050	60	45	15	6	..	12	22	..
1/17/40	..	....	.....	.....	13,200	50	43	7	3	2	16	29	..
1/20/40	..	....	.....	.....	7,250	58	42	16	4	..	8	30	..
1/21/40	..	....	.....	.....	6,450	57	43	14	3	..	5	35	..
1/26/40	95	14.6	4,860,000	375,000	11,100	54	37	17	8	..	10	28	..
1/31/40	99	15.2	4,920,000	480,000	9,200	60	42	18	5	1	6	28	..

During the height of the reaction, from December 26 to Jan. 6, 1940, the white blood cells of the peripheral blood showed some interesting changes. Relative leukopenia persisted until January 3, and a decided granulocytopenia was present until January 9, fourteen days after entry to the hospital. The white blood cell count varied from 5,950 to 9,200 per cubic millimeter, even though the body temperature was considerably elevated during that period. The polymorphonuclear cells varied from none on Dec. 29 and 31, 1939 to 25 per cent on Jan. 5, 1940. From January 14 until discharge from the hospital, on January 23, the number and type of granulocytes were within normal range. The eosinophils reached their greatest number three days after entry (18 per cent). Metamyelocytes appeared in the peripheral blood from the ninth to the sixteenth day of hospitalization. Before and after this time no myelocytes were seen. Blood counts made after dismissal from the hospital showed a normal picture (table 1).

Examination of Bone Marrow.—Specimens of bone marrow were obtained by aspirations of sternal marrow and were examined. Table 2 shows the results.

Study of the aspirated marrow from the sternum showed interesting cytologic features. It will be noted that the myeloblasts and myelocytes were considerably increased. The myelocytes totaled 27 per cent, whereas the normal is from 4.5 to 8.6 per cent for neutrophilic and 0.3 to 1 per cent for eosinophilic myelocytes. The significance of 13 per cent of eosinophilic myelocytes is not clear, but the obvious suggestion is that it may indicate an allergic reaction involving the marrow. The arrest of maturation, as indicated by the high percentage of myelocytes, was at the myelocyte level. No neutrophilic polymorphonuclear leukocytes were found in the initial marrow study. The high monocyte and plasma cell percentage is of interest, and one cannot escape the suspicion that these cells had wandered into the marrow with the onset of granulocytopenia. Two weeks after the first marrow

TABLE 2.—*Data on Bone Marrow Obtained by Sternal Puncture*

	December 28, 1939	January 11, 1940
Myeloblasts	3.5	..
Myelocytes		
Neutrophil	14 }	11
Eosinophil	13 }	
Metamyelocytes		
Neutrophil	..	15
Eosinophil	5.5	..
Polymorphonuclear neutrophils		
Nonfilamented	..	40
Filamented		
Eosinophil	5.5	3
Basophil	1.5	1
Lymphoblasts	1	..
Lymphocytes	12	12.5
Proerythroblasts	5	..
Erythroblasts	13	5
Monocytes	18	12.5
Plasma cells	8	..
Total counted	100	100

studies, the second specimen was aspirated and showed a normal cellular picture except for the percentage of neutrophilic myelocytes, which was still high.

Effects of Mapharsen Therapy.—In view of a recent report by Goldberg [6] of a patient who had tolerated mapharsen without untoward effects after having recovered from a granulocytopenic reaction due to neoarsphenamine and our own experiences with mapharsen in patients who had thrombopenic purpura, it was decided to give this patient mapharsen. It should be recalled that he was suffering with early syphilis, and the need of arsenic was urgent. On January 12, seventeen days after entry to the hospital and three and a half weeks after his last injection of neoarsphenamine, he was given 0.005 Gm. of mapharsen; three days later, 0.02 Gm.; three days after this, 0.04 Gm.; eight days later, 0.06 Gm., and five days later, 0.06 Gm., without any untoward reaction.

6. Goldberg, M.: Mapharsen as a Substitute for Neoarsphenamine in Agranulocytic Angina in a Pregnant Syphilitic Woman, Am. J. Syph., Gonor. & Ven. Dis. **23**:79 (Jan.) 1939.

Table 3 shows the results of the blood counts during the first four injections of mapharsen.

The blood counts on January 26 and January 31 were made at the office clinical laboratory of one of us (E. H. F.) after the patient left the hospital and preceded the injections of mapharsen given on those dates.

TABLE 3.—*Blood Counts Before and After Administration of Mapharsen in a Case of Granulocytopenia Following Neoarsphenamine Therapy*

Date	Red Blood Cells per Cu. Mm.	Hemoglobin, per Cent	Hemoglobin, Gm.	White Blood Cells per Cu. Mm.	Polymorphonucleears	Filamented Nonfilamented Ratio	Eosinophils	Basophils	Lymphocytes	Monocytes	Platelets	Comment
1/12/40	5,400,000	104	14.25	15,200	53	41-12	2	..	34	10	350,000	Before mapharsen 0.005 Gm.
				15,200	56	46-10	2	1	29	12	520,000	15 min. after mapharsen 0.005 Gm.
				16,400	66	58- 8	2	..	24	8	640,000	30 min. after mapharsen 0.005 Gm.
				16,800	63	55- 8	..	..	31	6	440,000	1 hr. after mapharsen 0.005 Gm.
				17,600	66	56-10	1	1	27	5	400,000	2 hr. after mapharsen 0.005 Gm.
1/15/40	5,510,000	104	.....	11,200	68	55-13	1	..	25	6	480,000	Before mapharsen 0.02 Gm.
				10,400	66	58- 8	2	1	23	8	490,000	15 min. after mapharsen 0.02 Gm.
				10,200	61	45-15	1	1	23	13	590,000	30 min. after mapharsen 0.02 Gm.
				13,100	70	60-10	..	..	21	9	580,000	1 hr. after mapharsen 0.02 Gm.
				14,600	66	54-12	1	1	30	2	500,000	2 hr. after mapharsen 0.02 Gm.
1/18/40	5,590,000	104	.....	11,500	60	31- 9	3	1	30	6	610,000	Before mapharsen 0.04 Gm.
				11,900	59	52- 7	..	..	22	12	580,000	15 min. after mapharsen 0.04 Gm.
				12,600	57	50- 7	2	1	32	8	500,000	30 min. after mapharsen 0.04 Gm.
				11,800	45	43- 2	3	2	44	6	620,000	1 hr. after mapharsen 0.04 Gm.
				12,100	66	54-12	1	..	31	2	570,000	2 hr. after mapharsen 0.04 Gm.
1/26/40	4,860,000	95	14.6	11,100	67	.....	5	..	28	..	375,000	Before mapharsen 0.04 Gm. (office)
1/31/40	4,920,000	99	15.2	9,200	64	.....	5	..	30	1	480,000	Before mapharsen 0.06 Gm. (office)

From January 31 to May 4 the patient received eleven injections of mapharsen of 0.06 Gm. each and five injections of bismuth salicylate of 0.2 Gm. each, without any untoward reaction.

COMMENT

The effect of neoarsphenamine on the formed elements of the peripheral blood apparently differs qualitatively from that of mapharsen in that mapharsen causes less disturbance in the normal ratio of white blood cells and platelets. Although we have not determined this fact definitely from an analysis of our material, there are indications that this will be substantiated by continued careful study.

Study of the patient with granulocytopenia following neoarsphenamine was extremely interesting. The mechanism of this reaction is quite different from the development of thrombopenic purpura. In the latter there are a rapid diminution in the number of the platelets in the peripheral blood and, presumably, capillary dilatation. It is not probable, because of the rapidity with which the platelets disappear from the circulation, that they are destroyed. It is more likely that they leave the larger vessels and enter greatly dilated capillaries. Although capillary fragility is increased during the thrombopenic reaction and persists for some time after the platelet count is restored to normal, there is considerable doubt that the capillary endothelium is actually injured. With the thrombopenia following arsphenamine therapy there is no injury to the bone marrow.

The granulocytopenic reaction, on the other hand, is due to a toxic action of the drug on the granulocytic elements of the bone marrow. In some manner the drug interferes with maturation of these cells, and the polymorphonuclear neutrophilic leukocytes soon disappear. Arsphenamine appears to act in this regard similarly to such chemicals and elements as gold, aminopyrine, sulfanilamide and benzene. In the case reported here the maturation of the granulocytes in the bone marrow was arrested at the level of the neutrophilic and eosinophilic myelocytes. It is also interesting to note that these myelocytes did not enter the peripheral blood early in the course of the reaction but did so later, when the polymorphonuclear cells began to increase in the peripheral blood. The presence of a large per cent of eosinophilic myelocytes in the bone marrow suggests a possible allergic background to this reaction.

While the mechanism of the granulocytopenic reaction is entirely different from that of thrombopenia, it is similar in some respects to that of the aplastic anemia which follows administration of arsphenamine. Both represent an injury to the bone marrow. In granulocytopenia only a single element is affected, while in aplastic anemia all the elements of the bone marrow are disturbed.

The fact that mapharsen did not cause a reproduction of granulocytopenia in the case reported here or thrombopenic purpura in our other cases of blood dyscrasia is of considerable clinical importance. It indicates that mapharsen is less likely to produce these two blood dyscrasias than are the arsphenamines and that a cautious trial of this drug is justified for patients in whom either of these reactions has developed after arsphenamine therapy if the need of arsenic is apparent. On the other hand, use of mapharsen is not without potential danger, as we have seen it produce aplastic anemia in 1 of our patients. Rein and Wise [7] reported an instance of aplastic anemia following mapharsen

7. Rein, C. R., and Wise, F.: Mapharsen in the Treatment of Syphilis in Office Practice, J. A. M. A. **113**:1946 (Nov. 25) 1939.

therapy which terminated fatally. Aplastic anemia is by far the most serious of blood dyscrasias and should be watched for in patients undergoing mapharsen therapy.

SUMMARY AND CONCLUSIONS

A brief review of our experiences with thrombopenic purpura following arsphenamine therapy is presented. These experiences indicate that mapharsen usually will not cause a reproduction of this reaction in patients exhibiting this type of blood dyscrasia. Vitamin C in large amounts did not alter the tendency to this reaction in patients sensitive to arsphenamine.

In 30 patients who tolerated antisyphilitic treatment without untoward reaction, neoarsphenamine caused a diminution in the leukocytes and platelets of the peripheral blood. Study of our data indicated that mapharsen is much less likely to produce these changes.

A case of granulocytopenia following neoarsphenamine is described in detail, with a description of the blood and bone marrow changes. The patient tolerated mapharsen without untoward reaction.

ABSTRACT OF DISCUSSION

DR. CHARLES C. DENNIE, Kansas City, Mo.: The part of this paper that I shall discuss is that which deals with the effect of neoarsphenamine and mapharsen on the hemopoietic organs and their products in the treatment of congenital syphilis.

My associates and I were asked to determine the effect of mapharsen on the blood of children. We selected 20 children with congenital syphilis and gave each ten doses of mapharsen at weekly intervals. Before administration of each dose a blood count was made, and half an hour afterward another blood count was made. A complete chemical examination of the blood of these patients was made after the first, fourth, seventh and tenth dose.

We found this fact consistent: Mapharsen reduces the white cell count considerably, at the expense of the polymorphonuclear leukocytes. The total white cell count is sometimes reduced to as low as 3,500 per cubic millimeter. This reduction was obviated to some extent during the midcourse of the treatment. At the end of the course of treatment the count would be higher than it was in the midcourse. It took from three to six weeks for the blood count to rise anywhere near the normal level. In no case did it ever rise quite to the normal level again.

On the other hand, the blood chemistry was in no way changed, except at Christmas, when the level of blood sugar was a little higher.

Similar experiments with neoarsphenamine showed a slight decrease in the white cell count, not at the expense of the leukocytes. The patients given neoarsphenamine all regained the normal cell count at termination of the treatment.

Of course, thrombopenia and granulocytopenia are two entirely different conditions. In one the system of histiocytes is probably involved. That includes, as is known, the cells lining the capillaries. When one makes a histologic examination of tissues removed from patients with arsenical dermatitis who also have hemorrhages in the skin, one finds that the endothelial linings of the small blood vessels are desquamated, and in many cases the vessels are ruptured.

This can be seen particularly in the lining of the bronchial tubes, which seems to indicate that there is a paradoxic therapeutic reaction.

DR. LAWRENCE G. BEINHAUER, Pittsburgh: My associates and I have been interested for the past two years in the effect of the heavy metals on the hemopoietic system, and I wish to confine my remarks to the effects of gold.

We have had 3 cases of thrombopenic purpura due to injection of a gold compound. Because of this, we carried out a series of experiments on animals. Over a period of eighteen months we gave a series of rabbits a unit dose of gold equivalent per kilogram of body weight to the average dose given to man. After a time we noticed a decided reduction in the red blood cell count. One animal had slight purpura; it was killed, and autopsy was performed. There were definite changes in the endothelial linings of the capillaries of the peripheral vascular system, whereas the hemopoietic system revealed no abnormality. This may have some bearing on the remarks made by Dr. Dennie.

DR. NORMAN N. EPSTEIN, San Francisco: The value of investigations of this kind is entirely dependent on the accuracy of the hematologic work. This part of the work was conducted by Dr. Falconer.

Dr. Van Studdiford's discussion of the report of mapharsen and arsphenamine dermatitis by Dr. Schoch and his associates pertains to this paper also.

It may be that there will be some misinterpretation of the conclusions drawn here, but still I think one must recognize that there are certain essential differences in the reactivity of the arsenical preparations used in the treatment of syphilis. Only when an arsenical is absolutely needed for the possible cure of the patient would we recommend its trial after the development of the blood dyscrasias described in this paper.

I was interested in Dr. Dennie's remarks in regard to the effect of mapharsen on the peripheral blood of congenitally syphilitic children. Our observations on adults were somewhat at variance with his. We found that mapharsen had much less effect on the peripheral blood of adults than had neoarsphenamine.

There is still considerable doubt whether the drug actually injures the capillaries or whether there is dilatation of the capillaries produced by the action of the drug, allowing blood cells to escape into the surrounding tissues.

We firmly believe that the platelets are not destroyed during thrombopenia following neoarsphenamine therapy, because one can send them back into the blood stream promptly by an injection of epinephrine. The rapid restoration of the platelets to a normal number would also seem to indicate that they are not destroyed.

There is a point that I should like to clarify in my discussion of the paper of Dr. Schoch and his co-workers, in which they stated that there had been reports of desensitization to neoarsphenamine by repeated intravenous injection of small doses of the drug. In this group of blood dyscrasias the sensitization increased greatly after repeated doses of the drug. The sensitization in some instances seemed to decrease in varying degrees after administration of the drug was stopped, but the patient never became completely desensitized.

I believe that repeated injections of neoarsphenamine in patients who are already sensitive to the drug will tend to increase their sensitivity.

MAPHARSEN IN THE TREATMENT OF FORTY PATIENTS FOLLOWING ARSPHENAMINE DERMATITIS

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Our primary objective several years ago in starting this study was to evaluate the usefulness of a new drug of low toxicity, mapharsen, for patients who had recovered from arsphenamine dermatitis of varying grades of severity. Moore and Keidel [1] were the first to describe the procedure of intravenous testing. It is open to question whether intravenous testing is a desensitization procedure. Intravenous testing with mapharsen offered a new approach to this problem.

Foerster, McIntosh, Wieder, Foerster and Cooper,[2] in their excellent original article on the clinical use of mapharsen, were the first to report administration of mapharsen to a patient who had recovered from arsphenamine dermatitis. They reported a single incident in which mapharsen was administered to such a patient, one dose being given, with recurrence of the dermatitis. They observed no cases of severe exfoliative dermatitis resulting from the use of mapharsen alone in the original study, nor have they observed any since.[3]

Gruhzit and Dixon [4] reported their observations on 4,841 patients who received a total of 75,859 injections of mapharsen without the

Read at the Sixty-Third Annual Meeting of the American Dermatological Association, Inc., Colorado Springs, Colo., May 30, 1940.

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1. Moore, J. E., and Keidel, A.: Dermatitis and Allied Reactions Following Arsenical Treatments of Syphilis, Arch. Int. Med. **27**:716 (June) 1921.

2. Foerster, O. H.; McIntosh, R. L.; Wieder, L. M.; Foerster, H. R., and Cooper, G. A.: Mapharsen in Treatment of Syphilis: Preliminary Report, Arch. Dermat. & Syph. **32**:868-892 (Dec.) 1935.

3. Wieder, L. M.; Foerster, O. H., and Foerster, H. R.: Mapharsen in the Treatment of Syphilis: Further Experiences, Arch. Dermat. & Syph. **35**:402 (March) 1937. Wieder, L. M.: Personal communication to the authors.

4. Gruhzit, O. M., and Dixon, R. S.: Mapharsen in Mass Treatment of Syphilis in a Clinic for Venereal Diseases, Arch. Dermat. & Syph. **34**:432 (Sept.) 1936.

development of severe exfoliative dermatitis in a single case. In this series there were 46 cases of dermatitis attributed to mapharsen given in combination with mercury or bismuth compounds. They reported 1 case of severe exfoliative dermatitis following ten injections of mapharsen in a patient who recently had had a dermatitis due to neoarsphenamine.

Kulchar and Barnett [5] credited mapharsen with producing arsenical exanthems in 0.5 per cent of 1,270 injections. In 1 patient, who had an exfoliative dermatitis following neoarsphenamine, a single dose of mapharsen produced a recurrence of the dermatitis.

Miller, Epstein and Simpson [6] noted transient erythematous eruptions from mapharsen but not exfoliative dermatitis. They reported on 5 patients who recovered from exfoliative dermatitis due to neoarsphenamine, all of whom experienced a recurrence after taking mapharsen in 10 mg. doses. Patch tests with mapharsen on these 5 gave negative results, but the technic of patch tests was omitted in the report.

Cole and Palmer [7] observed 1 case of moderately severe dermatitis following the use of mapharsen alone. The dermatitis followed the first injection in the second course of mapharsen. They administered mapharsen to 4 patients after recovery from arsphenamine dermatitis; in 3 the dermatitis had been moderately severe, and in 1, severe. Immediate administration of mapharsen in doses of 5 to 20 mg. in the 3 cases of moderately severe dermatitis resulted in recurrence of the dermatitis in all instances. After a lapse of four to six months mapharsen was again administered to 2 of these 3 patients, successfully to 1 and unsuccessfully to the other. Administration of 5 mg. of mapharsen to the fourth patient, who had recovered from a severe dermatitis due to neoarsphenamine six years previously, precipitated another attack of exfoliative dermatitis.

Jordan and Traenkle [8] directed their attention specifically to the use of mapharsen for patients who had had reactions following administration of arsphenamines. They described 8 patients who had cutaneous reactions to other arsenicals. Two of their patients, who had had mild papular arsphenamine dermatitis, tolerated mapharsen in therapeutic doses. One patient, after recovery from severe crustaceous arsphenamine dermatitis, had a mild recurrence after the second injection of 10 mg. of mapharsen. Their 5 remaining patients exhibited cutaneous reactions which were urticarial, pruritic, fixed and plaquelike.

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5. Kulchar, G. V., and Barnett, C. W.: Mapharsen in the Treatment of Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **20**:482 (Sept.) 1936.

6. Miller, H. E.; Epstein, N. N., and Simpson, R. G.: Mapharsen: Its Use in the Treatment of Syphilis, California & West. Med. **45**:321 (Oct.) 1936.

7. Cole, H. N., and Palmer, R. B.: Mapharsen in the Treatment of Syphilis, Arch. Dermat. & Syph. **36**:561 (Sept.) 1937.

8. Jordan, J. W., and Traenkle, H. L.: Reactions to Mapharsen, with Special Reference to Its Use in Patients Who React to the Arsphenamines, Arch. Dermat. & Syph. **36**:1158-1164 (Dec.) 1937.

Epstein [9] warned against the use of any arsenical, including devegan [10] and carbarsone, in treating patients who are sensitive to the arsenical preparations used in antisyphilitic therapy. In the 6 cases reported, patch tests with various compounds of arsenic, including neoarsphenamine and mapharsen, gave positive reactions, but in none of these cases did Epstein attempt administration of mapharsen.

Astrachan and Wise [11] reported 19 minor dermatitides resulting from mapharsen in the treatment of 118 patients. Their report of 1 patient, who tolerated twenty-two injections of mapharsen after severe exfoliative dermatitis from neoarsphenamine, stands alone.

Stevenson and Chambers [12] reported 2 cases of arsenical dermatitis apparently precipitated by mapharsen. In 1 the condition was severe and in 1 it was moderately severe but both patients had previously received neoarsphenamine. The authors described another case of moderately severe arsenical dermatitis, due to neoarsphenamine, in which they gave an injection of mapharsen with no apparent reaction. No mention was made of the dose of mapharsen administered or of the number of treatments.

Chargin, Leifer and Rosenthal [13] commented on the rarity of cutaneous eruptions resulting from the use of mapharsen and reported no instances of severe exfoliative dermatitis in an experience covering 25,000 injections of the drug. They reported on 2 patients with recurrent toxicodermas from neoarsphenamine who were able to take mapharsen without difficulty.

Summarizing the aforementioned 17 cases gives the following results: After recovery from severe exfoliative dermatitis 1 patient tolerated mapharsen and 10 did not; after recovery from mild arsphenamine dermatitis 5 patients tolerated mapharsen and 1 did not.

Of special interest in connection with this study is the most recent report by Robinson,[14] of Baltimore. Robinson reported his experience

9. Epstein, E.: Sensitivity to Both Trivalent and Pentavalent Arsenicals, Arch. Dermat. & Syph. **36**:964 (Nov.) 1937.

10. According to the Winthrop Chemical Co., Inc., "devegan consists of acetylaminohydroxyphenylarsonic acid (acetarsone) and a substance obtained by subjecting carbohydrates to a partial transformation by mild oxidation and hydrolysis. A small amount of boric acid is also present." The product has not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

11. Astrachan, G. D., and Wise, F.: Further Experiences with Mapharsen: Its Use in Latent Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **22**:470 (July) 1938.

12. Stevenson, C. S., and Chambers, W. M.: Toxic Effect of Arsenical Compounds, U. S. Nav. M. Bull. **37**:687 (Oct.) 1939.

13. Chargin, L.; Leifer, W., and Rosenthal, T.: Mapharsen in the Treatment of Early Syphilis: Comparison of Results in One Hundred and Eighty-Eight Cases with Those of the Cooperative Clinical Group, Arch. Dermat. & Syph. **40**:208 (Aug.) 1939.

(Footnotes continued on next page)

at Moore's clinic with 110 patients who after recovering from arsphenamine dermatitis were intravenously tested with other arsphenamines. Eight patients yielded positive reactions to patch tests, although 2 of the 8 reactions were not strongly positive. Of these 2 patients, 1 did and 1 did not tolerate further arsenical therapy. Robinson reported failure with further arsenical therapy for the other 6, and his first conclusion reads as follows: "A strongly positive patch test (with papules, vesicles and edema) in a patient with a history of post arsphenamine dermatitis is a contra-indication to further treatment."

Special interest centered around a group of 33 of these patients who presented negative reactions to patch tests. "In 63 per cent of our negative patch tested cases the intravenous injection of 20 mg. of one of the arsphenamines produced a mild but conclusive dermatitis."

Sixty-three patients in Robinson's series, who were not given patch tests, were subjected to intravenous testing. The initial dose of arsphenamine, neoarsphenamine and silver arsphenamine was 25 mg., and of mapharsen, 5 mg. In this group there were 46 per cent failures, necessitating at least temporary discontinuance of arsenical therapy.

In 11 cases Robinson was finally able to resume routine treatment as a result of repeated intravenous testing, even in the face of mild recurrences. He interpreted this process in these 11 patients as possibly a desensitization procedure.

PLAN OF PRESENT STUDY

Almost all of the patients in this study were observed from the beginning of the original outbreak of arsphenamine dermatitis. Early treatment was instituted in almost every case with concentrated dextrose solution administered intravenously as suggested by Shaffer,[15] usually in combination with calcium gluconate. It is our impression that this type of treatment has greatly reduced the intensity and duration of cutaneous dermatitic complications.

Neoarsphenamine was the drug responsible for the original attack of arsphenamine dermatitis in all 40 patients.

The 40 cases have been subdivided into three groups.

In groups 1 and 2 the patients had an erythematopapular dermatitis clinically compatible with early arsphenamine dermatitis while under treatment for syphilis with neoarsphenamine. Those cases in which the dermatitis did not become generalized but involved only a portion of the body's cutaneous surface were classified as instances of grade I dermatitis (group 1). Instances of grade II dermatitis (group 2) included cases in which the dermatitis became generalized but did not progress

14. Robinson, H. M.: Intravenous Testing in Post-Arsphenamine Dermatitis, South. M. J. **29**:411 (April) 1936.

15. Shaffer, L. W.: Treatment of Post-Arsphenamine Dermatitis, Arch. Dermat. & Syph. **29**:173-188 (Feb.) 1934.

to the exudative or crustaceous stage. In groups 1 and 2 the patients were ambulatory.

Cases in which the dermatitis progressed to the exudative or crustaceous stage, necessitating hospitalization, were classified as examples of grade III arsphenamine dermatitis (group 3).

In groups 1 and 2 the dermatitis subsided promptly after withdrawal of neoarsphenamine, while in group 3 it progressed through the usual course.

The recommendation of the Cooperative Clinical Group [16] that a number of months should elapse between recovery from arsenical dermatitis and the beginning of further arsenical therapy has been utilized in this study. Of course, their suggestion that the type of arsenical used for further treatment be different from that which originally caused the dermatitis has been utilized.

Intravenous testing with neoarsphenamine or arsphenamine in doses of approximately one tenth of the therapeutic dose, as reemphasized by Moore, Woo, Robinson and Gay,[17] has been the procedure employed until this study was started. We have not attempted intravenous testing with arsphenamines with patients on whom a positive reaction to a patch test with neoarsphenamine (33 per cent) has been obtained. The dangers associated with intravenous testing of patients who have positive reactions to patch tests were pointed out several years ago by one of us (Schoch [18]).

In the present study patch tests have largely been omitted until after completion of the experiment. Warning as to the possibility of encouraging sensitization to the arsphenamines by early patch tests has been voiced by Beerman,[19] Stokes,[20] Bechet [21] and Jordan and Osborne.[22]

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16. Cole, H. N.: Cooperative Clinical Studies in the Treatment of Syphilis: Arsenical Reactions, Ven. Dis. Inform. **14**:173-200 (Aug.) 1933.

17. Moore, J. C.; Woo, S. T.; Robinson, H. M., and Gay, L. N.: Reactions of the Skin Following the Intradermal Injection of Arsphenamine, Arch. Dermat. & Syph. **23**:74 (Jan.) 1931.

18. Schoch, A. G.: Arsphenamine Sensitization Tests, Including a Report of Arsenical Dermatitis Due to the Arsenobenzol Radical of Bismarsen (Bismuth Arsphenamine Sulphonate), Am. J. Syph. **14**:75 (Jan.) 1930; The Patch Test and the Element of Syringe Contamination in Arsphenamine Sensitization Dermatitis, J. A. M. A. **98**:1367 (April 16) 1932; Arsphenamine Dermatitis: Attempted Sensitization to Neoarsphenamine and Further Observation on the Patch Test, Arch. Dermat. & Syph. **30**:672 (Nov.) 1934.

19. Beerman, H.: The Patch Test in the Determination of Arsphenamine Sensitization, Pennsylvania M. J. **39**:690 (June) 1936.

20. Stokes, J. W.: Modern Clinical Syphilology, ed. 2, Philadelphia, W. B. Saunders Company, 1934, p. 493.

(Footnotes continued on next page)

In the present series of 40 patients, patch tests were made on 13 prior to the beginning of treatment with mapharsen, and on 27 no patch tests were done until after completion of the experiment. Of the 13 patients, none were excluded from this study because of a positive reaction to the patch test.

RESULTS OF THE PRESENT STUDY

Fixed eruptions, plaquelike dermatitis, urticaria and erythema multiforme, due to neoarsphenamine, were not included in this study.

The average initial dose of mapharsen in groups 1 and 2 was 6.4 mg. The minimum initial dose in groups 1 and 2 was 0.6 mg., and the maximum initial dose in these groups was 20 mg. In group 3 the average initial dose was 1.1 mg. In this group the initial dose of mapharsen varied from a minimum of 0.1 mg. to the maximum of 5 mg. administered to 1 of the 10 patients in this group (grade II recurrence).

In groups 1 and 2, a total of 30 cases, mapharsen was tolerated in therapeutic doses in all but 3. Of the 3 patients, none had a dermatitis which precluded further administration of mapharsen. One patient died of tuberculous meningitis after having tolerated seven injections of mapharsen, with a maximum dose of 20 mg., and the drug had to be discontinued in the cases of the other 2 patients because of gastrointestinal intolerance.

Of 10 patients in group 3 the reverse was true. All were intolerant to the drug. All exhibited recurrences of the dermatitis varying from grade I to grade III in severity. Recurrence of the dermatitis was precipitated in all 10 patients by a dose of mapharsen of 5 mg. or less.

After administration of mapharsen to all patients, patch tests were made on these patients with neoarsphenamine (33 per cent solution) and mapharsen (3.3 per cent) as originally described by one of us (Schoch [18]).

The next step was to test their tolerance for neoarsphenamine. Four of 12 patients did not tolerate neoarsphenamine in therapeutic doses in group 1, but 8 did. Administration of neoarsphenamine was discontinued because of recurrence of the dermatitis in 3 of the 4 patients and because of a severe nitritoid reaction in the fourth.

Of the 14 patients tested intravenously with neoarsphenamine in group 2, 12 demonstrated intolerance to neoarsphenamine, 8 had a recurrence of the dermatitis (57 per cent), 3 had gastrointestinal reactions

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21. Bechet, P. E.: The Patch Test: An Evaluation of Its Possible Dangers. New York State J. Med. **39**:829 (April 15) 1939.

22. Jordan, J. W., and Osborne, E. D.: Observations on Arsphenamine Dermatitis with Special Reference to the Reliability of the Patch Test, New York State J. Med. **35**:210 (March 1) 1935.

and 1 had a nitritoid reaction. This figure (57 per cent) is comparable with that recorded for Robinson's [14] failures in a group of 63 patients (46 per cent failures) on whom patch tests were not previously made.

None of the patients in group 3 were subjected to further therapy with neoarsphenamine, because of their extreme intolerance to small doses of mapharsen.

It appears that in groups 1, 2 and 3 the patients exhibited various grades of sensitivity to intravenous arsenical therapy. If one considers the patients in groups 1 and 2 as exhibiting mild or moderate sensitivity to the drugs and patients in group 3 as exhibiting a high degree of sensitivity to the drugs, the superior results obtained with mapharsen as compared to neoarsphenamine, particularly in group 2, confirm our previous impression that mapharsen is the drug of choice for any intravenous testing procedure.

RESULTS OF PATCH TEST WITH RELATION TO TOLERANCE OR INTOLERANCE TO NEOARSPHENAMINE AND MAPHARSEN

In groups 1 and 2 (30 cases) there were 8 cases in which the results of the patch test with neoarsphenamine were not in accord with clinical observation. There were 18 in which the clinical observations were in keeping with the results of patch tests with neoarsphenamine. In the remaining 4 cases there were no data. In groups 1 and 2, 3 of 26 patients gave false positive reactions to patch tests with neoarsphenamine (cases 10 and 11 in group 1; case 10 in group 2).

In group 3 all 10 patients gave positive reactions to patch tests with both neoarsphenamine and mapharsen. These 10 patients all exhibited extreme cutaneous intolerance to mapharsen and were not further tested with neoarsphenamine intravenously.

Of the 30 cases in groups 1 and 2, the patch test with mapharsen was doubtful in 2 and negative in 26. There were no data on 2.

Since 1930 we have considered significant only positive reactions,[18] that is, reactions in which the patch test was frankly vesicular in amplitude, and have regarded doubtful and negative reactions together as not indicative of decided cutaneous hypersensitiveness to the drug. We have had no reason to change our attitude in this matter.

Sulzberger [23] suggested 1 per cent solution of neoarsphenamine for the patch test. In our experience, this concentration has been adequate in some instances to produce vesicular reactions on extremely sensitized patients. We still prefer using 33 per cent solution of neoarsphenamine, probably because of our greater familiarity with the use of this concentration for test patients and normal controls.

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23. Sulzberger, M. B.: Dermatologic Allergy, Springfield, Ill., Charles C. Thomas, Publisher, 1940, p. 456.

In groups 1 and 2, therefore, none of the patients gave a false positive reaction to the patch test with mapharsen, and all but 3 tolerated mapharsen in therapeutic doses (case 3, group 1; cases 4 and 9, group 2).

In group 3, 10 patients reacted positively to patch tests with mapharsen, and all 10 demonstrated their intolerance to the drug as evidenced by recurrence of the dermatitis (grade I to grade III).

It appears from these data that patch tests with neoarsphenamine serve only as a rough guide to further treatment with neoarsphenamine. The patch test with mapharsen is a much better and more reliable test than that with neoarsphenamine.

The mapharsen patch test does not in any way indicate the possibility of tolerance to further treatment with neoarsphenamine. Ten patients in groups 1 and 2, with negative reactions to mapharsen, demonstrated their intolerance to further therapy with neoarsphenamine by recurrence of the dermatitis.

There is some evidence, judging from the results of the patch tests with neoarsphenamine alone, that 5 patients in groups 1 and 2 were partially or completely desensitized by administration of one or more courses of mapharsen in small, gradually ascending doses. The patient in case 4 (group 1), prior to receiving a course of mapharsen, showed a doubtful reaction to a patch test with neoarsphenamine and a negative reaction later. In group 2, the patients in cases 12, 13, 15 and 16 showed a reduction in the amplitude of the reaction to the patch test after receiving mapharsen. Of these 5 patients, in 2 the reaction was reduced from doubtful to negative, and in 3, from positive to negative. These are the first examples in our experience in which positive reactions to patch tests with neoarsphenamine became negative when the test was repeated several months later. It is readily admitted that this change in cutaneous reactivity to the patch test could be spontaneous rather than due to any desensitizing effect of the course of mapharsen. Our data on this point are too meager to enable us to draw a definite conclusion. This observation, however, is in accordance with Robinson's [14] experience with 11 patients subjected to repeated intravenous testing.

We are not unduly apprehensive of the possible sensitizing effect of patch tests, as are others. In the future we plan to use patch tests with neoarsphenamine and mapharsen prior to administration of either drug after arsphenamine dermatitis, since it is our impression that the hazard of this procedure is small and the information obtained by it of distinct benefit.

SUMMARY

Forty patients, after recovery from arsphenamine dermatitis, were treated with small, gradually increasing doses of mapharsen. Of the 40 cases, 13 were classified as examples of grade I dermatitis (involving only a portion of the body surface); 17 as examples of grade II der-

TABLE 1.—*Group 1: Patients with Grade I Dermatitis (Mild, Not Generalized)*

No.	Race, Sex and Age of Patient	Dose and No. of Injections of Neoarsphenamine Precipitating Dermatitis	Patch Test (33% Neoarsphenamine)	Mapharsen			Interval in Mo. from Dermatitis to First Mapharsen Injection	Patch Test (33% Neoarsphenamine)	Patch Test (3.3% Mapharsen)	Mapharsen Tolerated in Therapeutic Doses	No. of Injections of Neoarsphenamine and Dose Tolerated	Reaction to Neoarsphenamine	Comment
				Initial Dose	Maximum Dose	Total No. of Doses							
1	W; F; 32	27 (0.6 mg.)	.....	0.6 mg.	60 mg.	18	53 mo.	Doubtful	Negative	Yes	1 (0.3 mg.)	Nitritoid grade III reaction after 2d injection (0.3 mg.)	Grade I recurrence after mapharsen 20 mg.; none later
2	N; F; 24	12 (0.45 mg.)	.....	10 mg.	40 mg.	12	7 mo.	.....	.....	Yes	.....	.....	Moved from city; all follow-up attempts failed
3	N; F; 22	5 (0.6 mg.)	.....	5 mg.	20 mg.	12	14 mo.	Negative	Negative	No	1 (0.1 mg.)	Grade I recurrence; 2 injections (0.2 mg.)	Pruritus and gastrointestinal reaction from mapharsen
4	N; F; 26	8 (0.6 mg.)	Doubtful	20 mg.	40 mg.	4	2 mo.	Negative	Negative	Yes	8 (0.6 mg.)	Gastrointestinal only	No dermatitis from mapharsen or neoarsphenamine; gastrointestinal reaction after mapharsen
5	N; F; 35	3 (0.6 mg.)	Positive	5 mg.	60 mg.	14	6 mo.	Positive	Negative	Yes	3 (0.1, 0.2, 0.2 mg.)	Grade II recurrence after 4th injection (0.2 mg.)	
6	N; F; 42	3 (0.45 mg.)	.....	0.6 mg.	40 mg.	12	4 mo.	Negative	Negative	Yes	8 (0.6 mg.)		
7	N; F; 45	9 (0.6 mg.)	.....	10 mg.	60 mg.	19	3 mo.	Negative	Negative	Yes	6 (0.45 mg.)		
8	W; F; 39	7 (0.6 mg.)	.....	0.6 mg.	60 mg.	20	4 mo.	Doubtful	Negative	Yes	6 (0.6 mg.)		
9	W; F; 33	11 (0.6 mg.)	.....	10 mg.	60 mg.	15	5 mo.	Doubtful	Doubtful	Yes	9 (0.6 mg.)	.....	First injection of neoarsphenamine 60 mg.; pruritus; no eruption
10	W; F; 37	5 (0.6 mg.)	.....	20 mg.	60 mg.	12	3 mo.	Positive	Doubtful	Yes	5 (0.6 mg.)	.....	Chronic eczema of ankles
11	W; F; 19	7 (0.6 mg.)	.....	10 mg.	60 mg.	8	6 mo.	Positive	Negative	Yes	2 (0.45 mg.)	.....	Neoarsphenamine administered postoperatively in another hospital; no recurrence
12	W; F; 30	4 (0.6 mg.)	Negative	0.6 mg.	60 mg.	12	3 mo.	Negative	Negative	Yes	10 (0.6 mg.)		
13	W; F; 27	3 (0.6 mg.)	.....	10 mg.	40 mg.	9	3 mo.	Positive	Negative	Yes	No	Two grade I recurrences after 2 injections (0.1 and 0.2 mg.)	Patch tests repeatedly positive to neoarsphenamine and negative to mapharsen

TABLE 2.—*Group 2: Patients with Grade II Dermatitis (Moderate Severity; Generalized)*

No.	Race, Sex and Age of Patient	Dose and No. of Injections of Neoarsphenamine Precipitating Dermatitis	Patch Test (33% Neoarsphenamine)	Mapharsen			Interval in Mo. from Dermatitis to First Mapharsen Injection	Patch Test (33% Neoarsphenamine)	Patch Test (3.3% Mapharsen)	Mapharsen Tolerated in Therapeutic Doses	No. of Injections of Neoarsphenamine and Dose Tolerated	Reaction to Neoarsphenamine	Comment
				Initial Dose	Maximum Dose	Total No. of Doses							
1	W; F; 20	10 (0.6 mg.)	Positive	0.6 mg.	40 mg.	12	4 mo.	Positive	Negative	Yes	No	1 injection (0.06 mg.); grade II recurrence	
2	W; F; 36	19 (0.6 mg.)	.....	10 mg.	60 mg.	24	2 mo.	Negative	Negative	Yes	2 (0.06, 0.2 mg.)	2 injections (0.6, 0.3 mg.); chills, nausea and vomiting	Neoarsphenamine discontinued
3	W; F; 30	6 (0.6 mg.)	.....	2.5 mg.	60 mg.	21	6 mo.	Positive	Negative	Yes	No	Grade I recurrence (60 mg.)	Patch test positive after first course of mapharsen, doubtful after second course
4	N; F; 43	9 (0.6 mg.)	.....	0.6 mg.	20 mg.	7	6 mo.	.....	.....	Yes No (20 mg.)	.....	.....	Died of tuberculous meningitis
5	N; F; 20	12 (0.45 mg.)	.....	10 mg.	60 mg.	14	5 mo.	Positive	Negative	Yes	No	Grade I recurrence with 1 injection; (0.1 mg.)	Proved syphilis of stomach; mild pruritus following first 7 injections of mapharsen
6	N; M; 33	12 (0.6 mg.)	Positive	0.6 mg.	60 mg.	12	15 mo.	Negative	Negative	Yes	1 (50 mg.)	Pruritus and stomatitis 3d injection (100 mg.)	Evidence of desensitization
7	N; F; 36	16 (0.3 mg.)	.....	0.6 mg.	60 mg.	9	19 mo.	Doubtful	Negative	Yes	No	Grade I recurrence (60 mg.)	Gastrointestinal reaction after mapharsen
8	N; F; 32	8 (0.6 mg.)	.....	10 mg.	40 mg.	24	15 mo.	Doubtful	Negative	Yes	3 (40, 40, 80 mg.)	Nitritoid	Neoarsphenamine discontinued
9	N; F; 33	8 (0.6 mg.)	.....	10 mg.	30 mg.	12	21 mo.	Doubtful	Negative	No	No	Nausea and vomiting after 30 mg. of neoarsphenamine	Severe nausea from 30 mg. of mapharsen
10	N; M; 17	4 (0.45 mg.)	.....	10 mg.	50 mg.	12	18 mo.	Positive	Negative	Yes	1 (0.1 mg.)	Nitritoid; 2d injection (0.1 mg.)	
11	N; F; 27	9 (0.6 mg.)	.....	10 mg.	30 mg.	12	10 mo.	Negative	Negative	Yes	1 (0.3 mg.)	.....	Dosage adequate based on weight
12	N; M; 24	7 (0.6 mg.)	Positive	0.6 mg.	60 mg.	12	5 mo.	Negative	Negative	Yes	3 (0.06, 0.1, 0.3 mg.)	.....	Evidence of desensitization
13	W; M; 48	9 (0.6 mg.)	Doubtful	5 mg.	60 mg.	12	3 mo.	Negative	Negative	Yes	1 (0.06 mg.)	Grade I recurrence (0.1 mg.)	
14	N; M; 41	11 (0.6 mg.)	Positive	10 mg.	60 mg.	7	3 mo.	Positive	Negative	Yes	1 (0.06 mg.)	Pruritus (0.2 mg.)	Neoarsphenamine 0.45 mg.; grade I recurrence
15	N; F; 29	4 (0.6 mg.)	Positive	0.6 mg.	60 mg.	11	4 mo.	Negative	Negative	Yes	4 (60-200 mg.)	Grade I recurrence, 5th injection	Evidence of desensitization
16	W; F; 30	3 (0.6 mg.)	Positive	3 mg.	40 mg.	14	6 mo.	Negative	Negative	Yes	.....	.....	Evidence of desensitization
17	W; M; 27	6 (0.6 mg.)	.....	2.5 mg.	60 mg.	12	13 mo.	Positive	Negative	Yes			

No.	Race, Sex and Age of Patient	Dose and No. of Injections of Neoarsphenamine Precipitating Dermatitis	Patch Test (33% Neoarsphenamine)	Mapharsen: Initial Dose	Mapharsen: Maximum Dose	Mapharsen: Total No. of Doses	Interval in Mo. from Dermatitis to First Mapharsen Injection	Patch Test (33% Neoarsphenamine)	Patch Test (3.3% Mapharsen)	Mapharsen Tolerated in Therapeutic Doses	No. of Injections of Neoarsphenamine and Dose Tolerated	Reaction to Neoarsphenamine	Comment
16	W; F; 30	3 (0.6 mg.)	Positive	3 mg.	40 mg.	14	6 mo.	Negative	Negative	Yes	.....	.....	Evidence of desensitization
17	W; M; 27	6 (0.6 mg.)	.....	2.5 mg.	60 mg.	12	13 mo.	Positive	Negative	Yes			

TABLE 3.—*Group 3: Patients with Grade III Dermatitis (Exfoliative)*

No.	Race, Sex and Age of Patient	Dose and No. of Injections of Neoarsphenamine Precipitating Dermatitis	Patch Test (33% Neoarsphenamine)	Mapharsen: Initial Dose	Mapharsen: Maximum Dose	Mapharsen: Total No. of Doses	Interval in Mo. from Dermatitis to First Mapharsen Injection	Patch Test (33% Neoarsphenamine)	Patch Test (3.3% Mapharsen)	Mapharsen Tolerated in Therapeutic Doses	No. of Injections of Neoarsphenamine and Dose Tolerated	Reaction to Neoarsphenamine	Comment
1	W; F; 40	3 (0.6 mg.)	Positive	2 mg.	5 mg.	11	126 mo.	Positive	Positive	No	.....	.....	Four grade 1 recurrences; mapharsen 2 to 5 mg.
2	W; F; 38	5 (0.6 mg.)	.....	5 mg.	5 mg.	1	18 mo.	Positive	Positive	No	.....	.....	Grade 2 recurrence following 1 injection of mapharsen; neoarsphenamine patch test precipitated grade 1 recurrence
3	N; F; 18	5 (0.6 mg.) (1 maph. 0.4 mg.)	Positive	1 mg.	1.2 mg.	3	15 mo.	Positive	Positive	No	.....	.....	Neoarsphenamine patch test 1% positive; mapharsen test 0.3% doubtful; grade I, II recurrence
4	W; F; 26	5 (0.6 mg.)	.....	1 mg.	5 mg.	7	18 mo.	Positive	Positive	No	.....	.....	Four recurrences, grade 1, precipitated by mapharsen
5	N; M; 50	7 (0.6 mg.)	Positive	0.1 mg.	0.6 mg.	5	80 mo.	Positive	Positive	No	.....	.....	Grade 2 and grade 3 recurrences
6	N; F; 27	16 (0.6 mg.)	Positive	0.1 mg.	0.1 mg.	5	7 mo.	Positive	Positive	No	.....	.....	Grade 1 recurrence
7	W; F; 31	3 (0.6 mg.)	.....	0.1 mg.	1 mg.	6	6 mo.	Positive	Positive	No	.....	.....	Neoarsphenamine patch tests positive in 3.3%; mapharsen patch test doubtful in 0.3%; both positive in greater concentration; grade 1 recurrence
8	N; F; 27	3 (0.6 mg.)	Positive	0.1 mg.	0.1 mg.	1	5 mo.	Positive	Positive	No	.....	.....	Grade 1 recurrence with reduction of granulocytes after mapharsen
9	W; M; 26	6 (0.6 mg.)	Positive	0.1 mg.	0.1 mg.	1	8 mo.	Positive	Positive	No	.....	.....	Grade 3 recurrence from 0.1 mg. mapharsen
10	W; F; 29	8 (0.6 mg.)	Positive	0.1 mg.	0.6 mg.	2	18 mo.	Positive	Positive	No	.....	.....	Grade 1 recurrence with mapharsen 0.6 mg.; focal flare-up of original patch test reaction

matitis (a generalized arsenical dermatitis which did not progress to the exudative stage), and 10 as examples of grade III dermatitis (crustaceous or exudative generalized dermatitis necessitating hospitalization). The total of 40 cases constitutes the basis of this study.

Of the 30 cases in groups 1 and 2, the patients in 27 tolerated mapharsen in full therapeutic doses. In 2 cases the drug was discontinued because of severe gastrointestinal reactions, and 1 patient died of tuberculous meningitis before the experiment was completed.

There were 10 patients who exhibited grade III dermatitis. All 10 patients exhibited cutaneous intolerance to mapharsen in doses of 5 mg. or less.

The results of patch tests with neoarsphenamine and mapharsen, largely carried out at the completion of the mapharsen therapy, indicate a rough correlation between the results of patch tests with neoarsphenamine and the probability of further neoarsphenamine tolerance, but the results of patch tests with mapharsen agreed closely with the clinical experience of tolerance of this drug in the three groups.

Inadequate data are presented to indicate that administration of mapharsen to patients after arsphenamine dermatitis, beginning with small doses and gradually increasing the size of the dose up to the full therapeutic amount, accomplishes desensitization to the arsenicals in some persons.

CONCLUSIONS

1. Mapharsen can usually be successfully administered to patients after recovery from arsphenamine dermatitis produced by neoarsphenamine, provided the dermatitis is of lesser severity than severe exudative exfoliative dermatitis necessitating hospitalization. The initial dose recommended is 1 mg. and should not exceed 5 mg.

2. Mapharsen cannot be administered successfully even in minute doses to patients who have recovered from severe exudative exfoliative dermatitis due to neoarsphenamine. In intravenous testing with mapharsen, if attempted, the initial dose should not exceed 0.1 mg.

3. Patch tests with mapharsen (3.3 per cent solution) are a more reliable guide to further therapy with mapharsen than are patch tests with neoarsphenamine.

ABSTRACT OF DISCUSSION

DR. FRED WISE, New York: I should like to have one point explained. It concerns the interval between the clearing up of the dermatitis resulting from an arsenical and the time at which administration of mapharsen was begun. The authors stated that one of the committees recommended several months. What does that mean? Does it make any difference whether one waits two months or six months?

Is it to be assumed that in a certain group of patients bismuth compounds and iodides could be given, say, for six months, and mapharsen tried after such a lapse of time?

DR. MARTIN T. VAN STUDDIFORD, New Orleans: When I read the program, I thought that this would be an important and interesting study, because the facts must be so plainly stated that physicians who attempt to use these drugs would be kept from causing therapeutic accidents.

At the Marine Hospital in New Orleans, my associates and I attempted to give one-tenth the usual dose of mapharsen to 3 patients who had previously suffered a generalized neoarsphenamine dermatitis. Two of these 3 patients had a severe reaction in two hours and went through another prolonged sickness. One patient had a relatively milder action which healed in ten days.

Dr. Wise mentioned the interval between reactions and renewed injections. Lately a Filipino was treated at the Marine Hospital for a fractured arm, and during the routine hospital procedure it was found that he had a positive Wassermann reaction. He was given a few injections of bismuth subsalicylate and then one of mapharsen and had a generalized reaction. He then remembered that he had had a generalized neoarsphenamine reaction fourteen years previously, while in the Philippines.

I wonder, therefore, how one can set up distinct lines so that this excellent paper will not be misconstrued by the general physician, who receives much of his knowledge of drugs from the reprints of the pharmaceutical houses. I believe that this paper is a step toward a good end, but I do not think it is plain enough to enable one to determine what is going to be a grade 1, a grade 2 or a grade 3 reaction and whether a reaction which one might consider grade 1 might not be a forerunner of a grade 3 reaction if treatment were continued.

DR. UDO J. WILE, Ann Arbor, Mich.: I should like to ask the authors whether any determinations were made of possible damage to the liver in the cases of the patients who reacted badly to mapharsen.

It is conceivable that those patients by whom mapharsen was well tolerated after small reactions from neoarsphenamine did not sustain severe hepatic damage. Tests of hepatic function might have thrown some light on that.

DR. HARRY R. FOERSTER, Milwaukee: I should like to ask the authors whether they considered that dermatitis due to neoarsphenamine in patients who subsequently tolerated mapharsen may have been attributable to the benzol ring in neoarsphenamine rather than to the arsenical radical. The benzol ring is present in a number of drugs that may be skin sensitizers, but it is not present in mapharsen, which is arsine oxide (metaaminoparahydroxyphenylarsine oxide). If that consideration is plausible, may cutaneous intolerance to mapharsen, reported in certain cases of severe arsphenamine dermatitis, be looked on as partly due to a nonspecific sensitization, such as occurs in cases of severe contact dermatitis?

DR. CHARLES C. DENNIE, Kansas City: I have heard nothing in this discussion about the role of vitamin C in the production of eruptions due to arsenicals and bismuth preparations. I should like to know whether any determinations of that kind were made and whether vitamin C was used in the treatment of mild dermatitis.

If a patient has had a severe arsenical dermatitis and is given the smallest dose of neoarsphenamine even ten to fifteen years after that time, he will probably have just as severe an attack as the previous one. It seems that the great majority of such patients are permanently sensitized.

Mention has been made of the phenol ring as a possible cause of arsenical dermatitis. It is a well known fact that tryparsamide is also a phenol ring prepara-

tion and that it is given in much larger doses than neoarsphenamine. Yet one practically never sees a case of arsenical dermatitis due to tryparsamide.

Dr. Loren W. Shaffer, Detroit: I should like to ask the authors how rapidly they increase the dose. Starting at 1 mg., for instance, of mapharsen, how many treatments are necessary before it is safe to give a full standard dose?

Dr. Norman N. Epstein, San Francisco: In regard to the desensitization of a patient by repeated small doses of neoarsphenamine, it has been my experience, in dealing with the blood dyscrasias, that repeated small doses of the drug increased the sensitivity rather than decreased it.

Dr. Arthur G. Schoch, Dallas, Texas: In answer to Dr. Wise, the interval between the original outbreak of the dermatitis and the beginning of mapharsen therapy varied from a minimum of three months to a maximum of almost 100. The average interval was well in excess of eight months. We could not correlate this interval with the possible tolerance to the drug.

I saw only 1 patient who had had a grade III dermatitis (nine years previously) and who at present still shows a strongly positive reaction to the patch test with neoarsphenamine and a negative reaction to that with mapharsen. This is the only example in my experience of a patient who has recovered from a grade III crustaceous dermatitis and exhibited a negative reaction to the patch test with mapharsen. I should expect failure in Dr. Van Studdiford's cases if he started with one tenth of the full therapeutic dose. That means a beginning dose of 6 mg., the full dose being 60 mg. This expectation, I think, would be borne out by the literature and also by our experience with dermatitis grade III. With dermatitis of this grade we started usually with 0.1 mg. We hazarded 1 mg. occasionally, but recurrence of the dermatitis was grade II or III. That taught us to start with the 0.1 mg. dose in such cases.

One patient who received 5 mg. as her initial dose had a grade III relapse lasting another six or eight weeks.

In answer to Dr. Wile, we performed no tests of hepatic function. We give intravenous dextrose routinely, as suggested by Shaffer, and the regimen for patients receiving arsenical therapy includes a high carbohydrate–low fat diet.

I, like Dr. Foerster, would like very much to know what the radical is that these patients are sensitive to. In my own mind I have considered it the arsenobenzol complex. Of course, in tryparsamide, a quinquivalent arsenical, there is not the same relation of the arsenic coupled to the benzene ring with arsenic having three valences. That might account for some variation.

Epstein recently reported on patients who were sensitive to all forms of arsenical, both quinquivalent and trivalent, as demonstrated by the patch test.

We have not used vitamin C, liver extract or vitamin B.

In answer to Dr. Shaffer, it usually required from a minimum of ten to a maximum of fourteen injections to proceed from 1 mg. to 60 mg. doses. We considered 40 mg. for a patient who weighed slightly over 100 pounds (45.4 Kg.) a full therapeutic dose, but in the main we administered up to 60 mg., which is the maximum therapeutic dose recommended for mapharsen.

Our experience with the blood dyscrasias has been different from Dr. Epstein's. We now have 3 patients with granulocytopenia and 1 with aplastic anemia who have recovered, all 4 of whom are now taking mapharsen apparently well.

We use as a guide the white blood cell count and the differential ratio. We started with a "homeopathic dosage" in dealing with the blood dyscrasias, but to date we have not observed the effect that Dr. Epstein described.

HERPES PROGENITALIS AS A VENEREAL CONTAGION

HERMAN SHARLIT, M.D.
NEW YORK

The infectious (virus) nature of many herpetiform eruptions has been established by the production in animals and in human beings of comparable reactions in skin or mucous membrane from inoculation with material from spontaneously evoked lesions. Concerning herpes febralis and herpes progenitalis, similar studies have led to the conclusion that their respective viruses are immunologically distinct, a distinction corroborated by the epidemiologic features of both.[1]

Long before a virus became suspected, nineteenth century clinicians of wide experience were sufficiently impressed with the persistent history of venereal disease in patients presenting genital herpes to surmise a venereal origin for the latter. Yet no single, unequivocal case history is recorded that establishes this clinical picture as a venereal contagion in its own right. For this reason the following short reports of 2 cases are recorded. The absolute reliability of the pertinent facts cogently argues acceptance of the theory of a venereal source of herpes progenitalis and suggests inclusion of this clinical entity in the group of venereal diseases.

REPORT OF CASES

In February 1928 a white man in his late thirties, while arranging his toilet immediately after sexual intercourse noticed a papule on the dorsal surface of the lower third of his penis. That night lightning pains developed in the right groin, and the next morning he observed a slight swelling in the right inguinal region. He appeared at my office that morning. Examination showed a solitary papule on the dorsal surface of the shaft of the penis, which on inspection with a magnifying lens suggested capping by a ruptured vesicle. The skin about the base of the papule was deeply red; a burning pain was present in the lesion, and pains radiated to the right groin. The right inguinal nodes were definitely enlarged and slightly but distinctly tender. The patient had never had a genital "sore" of any kind before.

In the preceding twelve months the patient had had sexual relations with only one woman (the one referred to later) with but a single exception, and that exception occurred just six days before his appearance at my office.

A dark field examination of this lesion showed no spirochetes. A Wassermann test of the woman "of a week ago" gave a negative result. She refused to permit examination of her genitals. A provisional diagnosis of genital herpes was made.

1. Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1932, vol. 11, p. 140.

Five days after his first visit the patient returned to the office, bringing with him the woman of his constant attention, the one with whom he had had sexual relations the night he observed the penile sore. At this visit the woman was the patient. The night before she had a burning pain in the right vulvar region, and in the morning at my office an eruption was revealed in that region. Examination showed a group of tiny vesicles on a deeply congested background on the right labium majus; the condition was typical herpes simplex, the first and only herpes progenitalis I had seen in a female. This patient had never had a genital lesion of any kind before.

To bring the record of both these patients up to the present: The woman's history extended for but one year from her first visit. During that time she had one recurrence of genital herpes, and that was in approximately the same region as that involved by the initial attack. The man's history has now been available for twelve years since his initial attack. During this time he has had at least a dozen recurrences of herpes progenitalis, on the shaft and on the corona. He has never again had a solitary papule covered by a vesicle but always grouped vesicles. The last two attacks, however, have been on the right buttock.

COMMENT

At the fourth meeting of the American Dermatological Association, in 1880, Greenough [2] read a paper on herpes progenitalis. He emphasized that in his experience genital herpes was seen only in males and that its inordinately high incidence in patients with histories of venereal disease and its further tendency toward recurrence after sexual intercourse led him to suspect a relation to venereal infection. Discussion of the paper brought out a difference of opinion as to any necessary relation to venereal infection, it being aptly pointed out that only persons who had had or suspected exposure to venereal disease consulted physicians for this harmless and transitory affliction. Duhring contributed to the discussion with the statement that he had never seen herpes progenitalis in a female. This statement impressed the elder Unna with the appropriateness of a contribution to an American journal on the subject of herpes progenitalis in women. Such a paper he contributed in 1883.[3] He pointed out that in his experience at the large Hamburg hospital for the care of prostitutes he had encountered many cases of herpes progenitalis. He statistically stressed the strong positive correlation between genital herpes and venereal infection, concluding that the sexual act was in some way responsible for the occurrence and recurrence of this vesicular eruption. Twentieth century medical literature fails to disclose any further clinical contributions to the epidemiology of herpes progenitalis other than Naegeli's [4] recent critical discussion of the biology of herpes simplex generally. He expressed the need for

2. Greenough, F. B.: Arch. Dermat. **5**:1 (Jan.) 1881.
3. Unna, P. G.: J. Cutan. & Ven. Dis. **1**:321 (Aug.) 1883.
4. Naegeli, O.: München. med. Wchnschr. **83**:339 (Feb. 28) 1936.

hesitancy in accepting the theory that herpes simplex is infectious in the ordinary meaning of the word. He called attention to the following clinical features of this infection that are not in accord with the expectations of a truly infectious disease: In spite of the frequency of this disease, the widespread susceptibility, the shortness of the incubation period as shown by experiments and the inevitable difficulty of controlling surface spread in cutaneous infections, there are no recorded cases of contagion or surface transfer.

However, the need for actual contact to cause an infection of the cutaneous surface may be greatly minimized in the presence of a ubiquitous organism against which a high degree of natural immunity exists. For the banal coccic infections of the skin or even for the virus infection of verruca vulgaris, one does not seek evidence of contagion to satisfy the conception of its infectiousness. However, herpes simplex, in almost limiting its appearance to cheeks, hands and genitals, demands in explanation something further than the concepts involved in local immunity of the skin or lack of it. Vaccination is something more than bringing a virus in contact with skin; it demands in addition preparation of the skin for acceptance with reaction (inoculation). And this preparation may be an intimate contact with an active lesion in some other person. In other words, initial eruptions of herpes simplex may require intimate cutaneous contacts with friction, etc., between a susceptible person and one with active lesions. This would readily explain the sites of predilection for eruptions of herpes simplex. Given, further, the probable general immunization of the skin after inoculation and the certain hardiness of the virus, there is a plausible explanation for the clinical features of the sites of choice, frequent recurrences and failure to spread the infection about the skin. But, as Naegeli pointed out, where are the evidences of contagious inoculation?

The cases reported herein are just such evidences, albeit apparently the first. Manifestly, it would be almost impossible, because of the promiscuous and frequent practice of kissing, to seek out adequate clinical evidence of the contagious inoculation of herpes labialis. With genital herpes, on the other hand, some degree of exactitude relative to the time and nature of a preceding contact, if any, can be expected and established. Nor should one in this connection ignore the question of exotic practices, occasional or habitual, that by contact inoculation may make possible the transfer of viruses from cheek to genitals or from genitals to face. Surely, the extremely exclusive location of this disease requires for the acceptance of a theory of contagious nature a more satisfactory elucidation of its epidemiology than has heretofore been offered. I have indicated the significance of these 2 case reports in connection therewith and see in them missing links in the chain of a

rationalized epidemiology. Rather than veer away from a belief in the truly infectious character of this disease, as Naegeli felt impelled to do, it behooves dermatologists to study more closely its epidemiology for discovery therein of the convincing evidence of its truly infectious status, as evinced by experimental data. It is hoped that members of the medical profession will make careful and detailed studies of the histories of their cases of herpes progenitalis to the end that these features of their epidemiology may be convincingly clarified. In the meantime I profoundly trust that none will be so rash as to challenge the claim of celibacy or to impugn the professions of chastity or fidelity on the prima facie evidence of herpes progenitalis.

It is strange that, in spite of the ease with which Unna found genital herpes in females, its recognition in a female patient about the city of New York has never been reported.[5] The Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, with the admission of 114,855 new cases from 1935 to 1939, inclusive, had in that period 45 cases of herpes progenitalis, all in males. Nor are reports available of the appearance of genital herpes in males before the age of sexual maturity.

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5. Dr. Charles Rein, of New York, who has had a large experience in the examination of female prisoners in the House of Detention stated the belief that he has encountered among them several cases of genital herpes. He was good enough to let me include in this report the pertinent facts of 2 cases from his private records. A woman who was receiving treatment for frequently recurring genital herpes married during this period of treatment. Nine months after the marriage an initial attack of penile herpes occurred in the husband and was followed by recurrences. The rarity of genital herpes minimizes the force of coincidence as explanatory of these 2 cases in connubium. The fact that the husband had approximately nine months of exposure before taking the infection has well understood immunologic significance.

Clinical Notes

DERMATITIS DUE TO MESQUITE WOOD

Report of a Case

C. Duncan Stewart, M.D., Corpus Christi, Texas

Although sensitivity to various woods is well known, a search of the literature failed to reveal a reported instance of dermatitis due to mesquite wood. However, Shelmire [1] stated that he has observed a patient with proved sensitivity to this wood. It was therefore thought advisable to record this case in order that mesquite could be added to the list of trees known to produce dermatitis venenata.[2]

The mesquite tree (Prosopis juliflora) belongs to the family Leguminosae, or pod-bearing trees. There are seventeen genera and over thirty species of pod bearers native to North America, the best known of which are the various species of locust trees. The mesquite is found in arid and semiarid regions, ranging from Texas to southern California and north to Colorado and Utah.

REPORT OF CASE

C. S. H., a white man aged 56, was first examined March 24, 1940, at which time he presented a mildly erythematous, scaly dermatitis of the eyelids of three weeks' duration. There was slight edema of the lids. With the use of soothing topical applications plus fractional roentgen ray therapy the dermatitis rapidly subsided. Patch tests were refused, and the patient was discharged as cured on April 2. On April 8 the patient returned with an acute vesicular eruption of the entire face. Questioning revealed that on the preceding day he had worked on a cabinet which he was building. A liquid cement and seasoned mesquite wood were the only materials handled. Patch tests were later performed with a number of plant oleoresins, with the liquid cement and with moistened mesquite sawdust. Only the test with sawdust gave a positive reaction. Since the patient has avoided working with mesquite wood there has been no recurrence of the dermatitis.

615 Medical Professional Building.

1. Shelmire, J. B.: Personal communication to the author.
2. Senear, F. E.: Dermatitis Due to Woods, J. A. M. A. **101**:1527 (Nov. 11) 1933.

WOOD TICKS

An Easy Method for Removal from Skin

Donald J. Wilson, M.D., Omaha

An article by Friedman [1] mentions several chemical methods of removing ticks from the skin. He used ether and stated that Wiener used turpentine. He also stated that tobacco juice and benzine have been recommended.

1. Friedman, R.: Wood Tick Simulating Pedunculated Tumor, Arch. Dermat. & Syph. **41**:887 (May) 1940.

If such drugs are not available, for instance, during a hike or a hunting or fishing trip, the following method is useful: Strike an ordinary household match. As soon as it flares, a vigorous shake of the hand extinguishes the flame. The hot match head is promptly applied to the caudal end of the tick. A few seconds later the tick has withdrawn his beak and can usually be easily picked off. Sometimes a second application is necessary.

If the match is still flaming when applied the tick is often killed and must be forcibly pulled off.

FISTULA FROM RETAINED DENTAL ROOT

JOSEPH M. SHELTON, M.D., WASHINGTON, PA.

Having read Montgomery's recent account[1] of 3 cases of fistulas from dead teeth simulating dermal epithelioma, I thought that the following case report might be of interest.

F. M., a white man aged 36, was referred to me on March 20, 1940 because of a small growth at the tip of the chin. The patient stated that all of his teeth had

Fistula from retained dental root.

been extracted in 1937 because of severe pyorrhea. About a year later a slightly tender swelling appeared over the point of the chin. This persisted until two weeks before the patient consulted me, when a small "blister" developed; this opened quickly, discharging a sticky mucopurulent material.

On examination, a firm bluish red nodule the size of a small pea was seen in the center of a crater-like depression at the tip of the chin. It was topped by a small sticky crust. Its appearance suggested either a granuloma pyogenicum or an epithelioma. However, in view of the history and the location of the lesion, I suggested that he return to his dentist for a roentgenogram of the lower alveolus. He then volunteered the information that he had just had a roentgenogram of the mandible taken by a qualified roentgenologist, with the report, "No pathologic

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From the Pittsburgh Skin and Cancer Foundation.

1. Montgomery, D. W.: Fistulas from Dead Teeth Simulating Dermal Epithelioma, Arch. Dermat. & Syph. **41**:378 (Feb.) 1940.

changes in mandible." In spite of this report, dental roentgenograms of the suspected lower right lateral incisor area were made, and a small spicule-like root fragment was found. This was removed with considerable difficulty by the dental surgeon, and the fistular tract was thoroughly curetted. Healing was complete within a week. There has been no recurrence to the time of writing (three months later).

I think that this case is of particular interest for two reasons: (1) the length of time elapsing between the supposedly complete extraction of the patient's teeth and the appearance of the nodule and (2) the negative report following a routine roentgenogram of the mandible. The latter is an important point since the usual roentgenogram of a mandible brings out the horizontal rami clearly but lacks distinct detail in the region of the mentum. For this reason, dental roentgenograms are a necessity in ruling out a retained dental root in this region.

Editorials

WILLIAM ALLEN PUSEY, M.D., 1865-1940

A Tribute to a Great Leader

In the death of Dr. William Allen Pusey American dermatology has lost one of its greatest leaders and one who at the time of his death was justly considered the dean of his specialty. The passing of Dr. Pusey is an incalculable loss to dermatology, to the profession of medicine in general, to the lay public and to his many admirers and friends.

It is hard to find suitable words to pay a tribute to this truly remarkable man. It is fortunate that during his life he had the satisfaction of knowing the high esteem in which he was held by his colleagues. The January 1937 issue of the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY was especially dedicated to him and contains sketches of different phases of his life by outstanding men in various fields of medicine. One sketch was written by his close friend the late Mr. Rufus Dawes. Any man would have been proud to hear such praise as that showered on him at the large banquet given in his honor at the Palmer House in Chicago in 1933. Though he was the guest of honor at many functions at home and abroad, probably none of the many tributes which he received pleased him more than the presentation of resolutions by the Chicago Dermatological Society in 1936 at a banquet given in his honor.

In this attempt to do honor to Dr. Pusey, his many achievements will not be given in detail. This has already been done in the aforementioned issue of the ARCHIVES.

Dr. Pusey was a Kentuckian whose family had come from Virginia and Maryland in pioneer days. His earliest American ancestors were Quakers who had migrated to America with William Penn. His father was a physician, and a cousin, Dr. Hodgen, was a famous surgeon and a President of the American Medical Association. Dr. Pusey showed his scholarly ability in college, having been valedictorian of his class at Vanderbilt University. With such a splendid background and with the possession of ambition, courage, honesty and a delightful personality, it is not surprising that he achieved great distinction in medicine. He was a talented man who would have been successful in almost any walk of life.

In 1893 Dr. Pusey came from Kentucky to Chicago, where he began the practice of dermatology. While he had no friends to help him at the beginning of his career, he had an excellent training in dermatology

as a result of graduate work abroad and in New York. His ability was quickly recognized, and in the following year he was made professor of dermatology in the College of Physicians and Surgeons, later the University of Illinois College of Medicine. He held this professorship for twenty years and then resigned, to the regret of his colleagues, feeling that a score of years was long enough for any one to serve. He was then made emeritus professor.

Dr. Pusey's fame as a dermatologist is secure if for nothing else than his pioneer work in the use of roentgen rays. He was the first in this country to use this agent for treatment of diseases of the skin, his first publication on this subject having appeared just forty years ago. His pioneer work required initiative and courage of a high degree, and many of the results which he obtained at this early date, as shown by photographs, were astonishingly good. He was also the first to use roentgen rays in the treatment of leukemia and Hodgkin's disease. One of Dr. Pusey's most practical and best known contributions to dermatology was the introduction in 1907 of solid carbon dioxide for the treatment of various diseases of the skin.

Dr. Pusey was a gifted and facile writer, his originality being evident in all his publications. His numerous literary contributions included textbooks and historical monographs on dermatology and syphilis, a book for the laity on the care of the skin and educational writings for the public on venereal diseases. One of his best nonmedical publications was the story of "The Wilderness Road to Kentucky: Its Location and Features."

One of the great things that Dr. Pusey did for dermatology and syphilology was to conduct negotiations whereby the American Medical Association took over the publication of the *Journal of Cutaneous Diseases,* whose sponsors were thereby relieved of a heavy financial burden. He was appointed Editor of the new publication, the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY, a position which he held for sixteen years with unusual distinction. At the time of his death he was Editor Emeritus.

Dr. Pusey was not only an able writer but also an excellent speaker. He was not an orator but was always a doughty opponent in debate. Owing to his courage, forceful manner and delightful humor he usually managed to make others see his point of view. It might be added that he was nearly always right. His judgment of men and affairs was remarkably keen, and the common sense he possessed was called "uncanny" by one of his biographers.

Dr. Pusey's distinguished career as a leader of organized medicine began with his being practically drafted to serve as president of the Chicago Medical Society. Later he received the highest honor which the profession could give him, the presidency of the American Medical Association, he being the only dermatologist who ever held this high

position. Dr. Olin West, in writing of his presidency, said, "The Association has had no more faithful, no more intensely earnest, active and efficient officer than he. His personality, his industry, his high ideals, his courage, his aggressiveness, his energy, his willingness to serve, his scientific knowledge, and his determination to be useful to the American Medical Association have all contributed to the marking of his official career as one productive to the Association itself and to all of its membership." In recent years Dr. Pusey used his talents and influence in fighting against the socialization of medicine as vigorously as he had previously worked to raise the standards of medical education.

In spite of his many activities in medicine Dr. Pusey found time to devote to various civic duties. He held numerous positions of responsibility; one of which he was particularly proud was membership in the executive committee of the National Research Council. He also took great pleasure and pride in serving as one of the eleven members of the executive committee of the Board of Trustees of the Century of Progress Exposition in Chicago. He was largely responsible for the success of its medical exhibit, which was organized under his direction.

During the World War he served as chairman of the committee on venereal diseases in the Surgeon General's office. Instead of wearing a uniform he preferred to travel about the country in civilian clothes on innumerable tours of inspection. As a mere major or even as a colonel of the medical corps in uniform he would not have been able to do much arguing with general officers in command of the camps. Dr. Pusey in his tactful and insistent way was able to accomplish a great deal for the good of the medical department and consequently for the military service in general.

Dr. Pusey possessed an unusual combination of forcefulness and tact. He had a kindly outlook on life and was especially kind to inexperienced and young colleagues. On numerous occasions at medical meetings when a young member would read a technical paper which no one could discuss, Dr. Pusey would rise to the occasion and help the situation by some tactful word of praise. As editor he occasionally accepted papers which were not quite up to his standard of excellence because the authors were young men who needed encouragement or perhaps lacked the opportunities afforded by large medical centers.

Dr. Pusey was an unusually courageous man who was not afraid to express his opinions. He hated sham and hypocrisy. He admitted that he did not mind receiving honors but objected to an unseemly scramble to obtain them. He thought that men who said they didn't care for honors and medals and the approbation of their fellow men were not truthful.

One source of Dr. Pusey's strength and his ability to make a host of friends was his delightful sense of humor. A former questionnaire

sent to all new members of the American Dermatological Association contained the query, "Have you any fad?" Dr. Pusey replied, "Heaven forbid." This did not mean that he had no other interests or forms of recreation besides dermatology. Indeed, he could hold his own with the average man in a game of golf or billiards.

One important source of Dr. Pusey's success was the devoted help and advice he received for so many years from his wife. In saying this I am merely quoting what he often proudly admitted in public.

Dr. Herbert Rattner, in his delightful sketch entitled "William Allen Pusey at Close Range," described Dr. Pusey "As a man of honor with high ideals, as a rare person who combines knowledge with philosophical humor, as a man of manifold achievement—a historian, writer, business man, loyal friend and companion, teacher, clinician, raconteur. He has been called a very human man, a leading physician with a combination of urbanity, scholarship and humor." I might add that Dr. Pusey was not only a most able and forceful man but a most kindly and sympathetic one who was greatly beloved by his colleagues. He richly deserved the many honors that came to him. It was, however, not his personal success that made him a great figure in medicine but something more intangible. It was the influence for good he exerted over his colleagues in dermatology as well as in the medical profession in general that made him great. His fame is secure. From the personal standpoint, those who knew him well cannot be reconciled for his loss. In my own case, he was the best friend I ever had in medicine next to my honored father.

Dr. Pusey, who died at the age of 74, is survived by his widow (formerly Sallie Warfield Cunningham) and by his brother, Dr. Brown Pusey, a distinguished ophthalmologist of Chicago.

HOWARD FOX.

Obituaries

LUDWIG OULMANN, M.D.

1875–1940

Ludwig Oulmann was born in Stuttgart, Germany, on June 2, 1875, the son of Theodore and Ida Epstein Oulmann. The father was an engineer whose major effort was the building of a railroad through the Black Forest. There were no physicians in the immediate family. The youth attended the Eberhard Ludwig Gymnasium in his native city. He took his medical degree from the Faculty at Wurzburg, later attended school at Erlanger (1895) and took postgraduate courses at Nurnberg and Berlin (1899 and 1900). While at college, he was released for his military service and was with the imperial forces in China during the Boxer Rebellion. For several years the young physician went to sea with the Hamburg American Line and saw the world as a ship's surgeon. These years served him well when he came to New York and was licensed to practice, on his twenty-ninth birthday. It is interesting to note that his admission to the New York Academy of Medicine on Dec. 3, 1908 antedated his membership in the New York County Medical Society by some three years.

Dr. Oulmann was always interested in the treatment of diseases of the skin and of syphilis. His training with Roentgen and his friendship with Paul Unna gave him opportunities to introduce into this country the advances of his foreign confreres. Thus, on his many trips to Europe he learned of new remedies and persuaded local firms to import them. Frequent meetings with Unna led to an untiring interest in histopathology.

Oulmann joined the staff of the German Hospital (now the Lenox Hill Hospital) and was on service all the rest of his life in New York. He was a member of the German Medical Society and at one time its president. He belonged to the Old German Student League and to the New York Section of the worldwide German literary and scientific organization, Schlaffaria. Dr. Oulmann was one of the earliest members of the Manhattan Dermatologic Society and was the oldest active member at the time of his death.

Interest in his homeland and an intense patriotism caused Dr. Oulmann much unhappiness during the trying days of 1914 to 1918. He was too outspoken for many, and his admiration for the Kaiser was too obvious for him to escape criticism and, indeed, suspicion. Delay in completing his application for citizenship likewise was misconstrued. It was not until after the armistice that he became an American citizen.

Dr. Oulmann wrote little for publication. He enjoyed discussion but always refused to edit copy properly for the printer. His hospital and office practice afforded him many opportunities for presenting cases. His hobby was to experiment at the compounding counter of his favorite druggist. Here he worked with powders and ointments, seeking color combinations to meet the complexion needs of his patients. He did not consider these excursions worthy of recording for posterity.

At the age of 43 Dr. Oulmann married, and his home life was ideal. Although childless, the seven years of companionship with Maria Josepha were most happy. A great change was noted in him after her death in Naples, Italy, in 1930. Failing eyesight, diabetes and cardiac failure then combined to cause a diminution in his professional activity. It was difficult to read the new journals and the fast appearing volumes of the *Handbuch*. But, it was the political changes abroad which weighed most heavily on the spirit of the man. Each successful encroachment led to further demands on the soul and the purse of Ludwig Oulmann. Relatives and friends of old Germany required aid to reach new lands. As these were overrun in turn by the invader, greater efforts were required to escape. No appeal was unheeded, and far places on the earth saw new faces due to Oulmann's gifts.

Few knew that these changes left deep scars on a man who had lived the life of a sincere, yes a devoted, German for many decades. He no longer attended certain festivities, avoiding mutual embarrassment. Despite this, he kept at his composing of German poems and a limited round of visiting with tried and true friends. To a very few intimates he confessed he was tired.

Dr. Oulmann died on Sept. 16, 1940. He is survived by a brother, Ernest, in this country, by another brother, Paul, in Naples, Italy, and by several nieces and nephews.

News and Comment

AMERICAN ACADEMY OF DERMATOLOGY AND SYPHILOLOGY

The third annual meeting of the American Academy of Dermatology and Syphilology will be held in the Palmer House, Chicago, Dec. 8 to 11, 1940. Registration will start Sunday morning, December 8. The special courses in histology, mycology, roentgen therapy, radium therapy and office photography will convene for six hours on that day. The clinical session will be held at the University of Illinois College of Medicine on Monday afternoon, December 9. There will be twenty-two clinical presentations covering all phases of dermatology and syphilology. There will be four symposiums on allergy, syphilis, pharmaceutical therapeutics and the physiologic and chemical aspects of the skin, each for three hours. A special feature will be a dermatopathologic round table discussion with a board of experts. There will be three guest speakers: Dr. Cyrus C. Sturgis on "Disease of the Blood and Blood-Forming Organs: Their Relation to the Skin and Mucous Membranes," Dr. William F. Petersen on "The Patient, His Skin and the Weather" and Dr. Elmer L. Sevringhaus on "Endocrine Glands and Their Relation to Dermatology."

Abstracts from Current Literature

EDITED BY DR. HERBERT RATTNER

LYMPHOGRANULOMA VENEREUM: TREATMENT OF 300 CASES, WITH SPECIAL REFERENCE TO THE USE OF FREI ANTIGEN INTRAVENOUSLY. BORRIS A. KORNBLITH, Am. J. M. Sc. **198**:231 (Aug.) 1939.

Kornblith reports the results of treatment in 207 cases of lymphogranuloma venereum with Frei antigen and in 93 cases with the use of palliative and surgical measures. Intravenous injections of Frei antigen gave good results in 95 per cent of the glandular cases and in 60 per cent of the cases of persistent genital lesions. In the cases of rectal involvement systemic and symptomatic relief were obtained, but surgical intervention is advised after the inflammation has subsided; temporary or permanent colostomy and dilation are suggested.

The human unfiltered antigen was administered three times weekly in a dose of 0.3 cc. In the majority of cases the first two treatments resulted in general reactions occurring after twelve hours and persisting for twelve to twenty-four hours; succeeding injections produced only headaches and malaise. In one fourth of the patients no untoward effects were noted from the beginning. In no cases were the reactions alarming.

BLOOD STUDIES IN LYMPHOGRANULOMA VENEREUM, WITH SPECIAL REFERENCE TO SERUM PROTEINS. R. H. KAMPMEIER, D. W. SMITH and R. M. LARSEN, Am. J. M. Sc. **198**:516 (Oct.) 1939.

The authors report studies in 67 cases of lymphogranuloma venereum showing that in 62 the serum protein was more than 8 Gm. per hundred cubic centimeters; in the remaining 5 cases the level was above 7.5 Gm. per hundred cubic centimeters. This elevation in serum proteins was chiefly due to hyperglobulinemia, since in 62 cases the serum globulin was 3 Gm. or more.

The authors observed these changes early in the course of the disease (in 1 case before the reaction to a Frei test became positive), but the increase was greater in cases in which the condition was of long standing. The change in the proteins appeared not to be related to the activity of the lesion.

Although the hyperglobulinemia is not a specific finding for this disease, it is constant and has some diagnostic value.

THE PSYCHONEUROGENOUS COMPONENT OF CUTANEOUS REACTION MECHANISMS. JOHN H. STOKES, HERMAN BEERMAN and NORMAN R. INGRAHAM, Am. J. M. Sc. **198**:577 (Oct.) 1939.

In an extensive review the general background is clearly outlined, as well as the difficulty in drawing valid clinical conclusions as to the relations between skin and psychoneurogenous elements. The authors point out numerous fields in which clinical and experimental research are indicated and would probably be productive of significant advances.

The relations of blood supply, vasomotor tone and secretory activity are discussed, but attention is also called to less clear but more interesting phenomena. The numerous fluctuant and variable allergic reactions to foods are discussed in relation to functional disorders of the gastrointestinal tract, particularly as modified by vagotonia and sympathicotonia. The sensation of itching is discussed in relation to threshold susceptibility, predisposing causes, direct causes and the intensification of attention to itching. Psychogenic influences on glandular secretion and on the

flush mechanism are also reviewed. The authors point out, too, that hypnosis and other psychogenous influences can alter the fundamental allergic background.

The entire article is thought provoking, and it is unfortunate that more knowledge is not available for review.

ANGINA PECTORIS IN HEREDITARY XANTHOMATOSIS. CARL MÜLLER, Arch. Int. Med. **64**:675 (Oct.) 1939.

The familial tendency of xanthomatosis is well known, but the frequent involvement of the cardiovascular system has been largely ignored. Müller examined or received information about 76 patients with xanthomatosis, members of seventeen families. Sixty-eight appeared to have had heart disease, confirming the observations of Harbitz and Montgomery. Cutaneous lesions had been noted in 38 persons, xanthoma tuberosum in 24 and xanthelasma in 14.

The author states that the syndrome of cutaneous xanthomatosis, hypercholesteremia and angina pectoris presents itself as a well defined clinical entity and as as a dominant hereditary disease. He suggests the possible value of prophylactic treatment in families subject to this condition.

SYPHILIS: A REVIEW OF THE RECENT LITERATURE. JOSEPH EARLE MOORE and CHARLES F. MOHR, Arch. Int. Med. **64**:1053 (Nov.) 1939.

It is likely that a few minutes spent in glancing at this review of the recent literature on syphilis will call to the attention of even the best read dermatologists a number of new developments which have been passed by at the time of their publication. Almost all the numerous subdivisions of syphilology are covered in the 75 pages of abstracts. In some cases editorial comment has been included.

THE PART PLAYED BY AGE AND THE FEMALE SEX HORMONES IN RESISTANCE TO INFECTION. DOUGLAS H. SPRUNT, Endocrinology **25**:625 (Oct.) 1939.

Sprunt reviews critically the influence of the endocrine pattern on the host's response to disease agents. As to the effect on antibody formation, he concludes only that antibodies develop in older animals more readily than in younger ones. With reference to allergic conditions and endocrine principles he states the belief that no definite conclusions can be drawn because of disagreement among the reports.

Of the morphologic changes resulting from injection of estrogenic substances only the following appear significant: those associated with gonococcic vaginitis in children, the prevention of peritonitis by the injection of amniotic fluid and the increased resistance of the gums to infection noted during pregnancy and as a result of estrogenic substances.

It is also thought that the dispersion or concentration of disease agents is affected by the endocrine pattern of the host and that this concentration or dispersion affects the host's resistance to disease.

THE RELATION OF THE ADRENALS TO THE RETARDED HAIR GROWTH IN UNDERFED ALBINO RATS. EARL O. BUTCHER and R. A. RICHARDS, Endocrinology **25**:787 (Nov.) 1939.

In underfed rats the adrenal gland hypertrophies and releases secretions which the authors regard as retardant of hair growth. Almost immediately after the removal of the adrenal glands of these animals a new growth of hair develops. The authors conclude that the adrenal gland is at least partly responsible for the retardation of hair growth in underfed animals, and they think it possible that the sudden growth of hair after adrenalectomy is due to the rapid passage of materials through the walls of the capillaries, the permeability of which has been increased as a result of the adrenalectomy.

AMOUNT AND DURATION OF IMMUNITY INDUCED BY INTRADERMAL INOCULATION OF CULTURED VACCINE VIRUS. T. M. RIVERS, S. M. WARD and R. D. BAIRD, J. Exper. Med. **69**:857 (June) 1939.

After observing a large series of vaccinations, the authors conclude that the amount of immunity produced by the cultured virus, as tested by means of a highly potent calf lymph vaccine virus, would probably not be considered sufficient for complete protection against smallpox. They suggest that primary vaccinations be made intradermally with their cultured virus and that revaccinations be made dermally six months to a year later with a potent calf lymph virus. Persons vaccinated in this way will not become sick and will not be subjected to the dangers associated with primary vaccinations with calf lymph virus, but will obtain a solid and lasting immunity to smallpox.

EXPERIMENTS ON HISTAMINE AS THE CHEMICAL MEDIATOR FOR CUTANEOUS PAIN. SOL ROY ROSENTHAL and DAVID MINARD, J. Exper. Med. **70**:415 (Oct.) 1939.

Rosenthal and Minard present experimental evidence that histamine is liberated when the upper layers of the skin are stimulated in the threshold range, although no gross or microscopic evidence of tissue damage is demonstrable. The amount of liberated histamine depends on the nature and intensity of the stimulus. They also demonstrated that histamine when injected intradermally or applied to the denuded skin neutralizes the action of the diffusates of stimulated skin and when injected subcutaneously or rectally abolishes generally the pain responses to pinching, pricking and cutting and lowers the electrical threshold of the skin decidedly, without affecting the somatic sensory nerve trunks. LYNCH, St. Paul.

CONTACT-REACTIONS IN ATOPY: I. CONTACT-REACTIONS TO SILKWORM IN ATOPIC SUBJECTS. MURRAY ALBERT and MATTHEW WALZER, J. Immunol. **38**:201, 1940.

During the course of routine cutaneous tests of atopic patients, the writers were impressed by the large percentage of positive reactions which were obtained with silkworm extract. This brought to mind previous findings of others "that most individuals could be easily sensitized to Ascaris lumbricoides by one or more intracutaneous or subcutaneous injections of a saline extract of this antigen. This suggested the possibility that silkworm, like the ascaris worm, might also be a potent sensitizer in humans. A large series of subjects were therefore injected intracutaneously and subcutaneously with varying amounts of silkworm containing 2.4 mg. Nøml., over periods of time ranging from one week to several months. It was found that sensitization to silk could not be induced by this procedure.

"The possibility that the sensitivity might be induced by prolonged application of the excitant to the surface of the skin was then investigated. Silkworm in a petrolatum base was applied in small amounts to the skin in a series of subjects. The technic employed was essentially the same as that routinely used for patch-testing in contact-dermatitis."

Albert and Walzer describe "A special type of contact-reaction to an oil-free preparation of silkworm. . . .

"This form of hypersensitiveness seems to occur most frequently in atopic children.

"It is not based upon the presence of atopic reagin and cannot be passively transferred to normal skin.

"The reaction is specific and may at times be induced by single or repeated applications of silkworm to the skin.

"The excitant is not the oil but is probably a protein.

"Dialyzed extracts of silkworm were found to contain the active excitant and produced positive contact-reactions."

CUTANEOUS REACTIVITY OF GUINEA PIGS TO GUM-ARABIC [ACACIA]. ROY M. SEIDEMAN, J. Immunol. **38**:237, 1940.

Seideman presents evidence of an allergic response to acacia (gum arabic) by cutaneous reactivity in both tuberculous and normal guinea pigs after repeated intracutaneous tests with tuberculin diluted with acacia. He shows that this sensitization is dependent on a true antigen-antibody reaction by positive anaphylactic and precipitin reactions.

"Although chemical analysis of gum-arabic points to the possibility of a protein fraction, further investigation is necessary to establish the chemical nature of the sensitizing fraction of acacia. Reports by other investigators call attention by inference to a protein or proteid substance, which is responsible for the antigenic activity of gum-arabic. The study calls into question the use of a tuberculin solution containing gum-arabic in epidemiological and immunological work."

CORNBLEET, Chicago.

DYSKERATOSIS OF DARIER, OF EXCLUSIVE ORAL LOCALIZATION. L. ABBATE, Arch. ital. di otol. **51**:520 (Oct.) 1939.

Darier gave the name psorospermosis to the disease described by him, but later investigators showed that it consisted of an abnormal and imperfect cornification of the epithelium. Nothing is known of the etiology or pathogeny of the disease, and treatment has had little influence on its course. It appears to be hereditary and familial, occurs in patients between the ages of 8 and 16 years and generally persists for life. Except for slight pruritus in some persons, it is subjectively symptomless. The sites of selection are the areas vulnerable to seborrhea. Oral localization has been previously observed, but only in association with widespread cutaneous lesions. On the hard palate the lesions are typical; in other oral areas, as the gums, cheeks and tongue, the type is somewhat modified. The typical lesion is an isolated, raised papule, umbilicated and cornified, but in the mucosa the papules form groups, with a slightly hyperemic base. Abbate observed the condition, limited to the mouth, in a man aged 50 who consulted him for mucous cysts of the nasal vestibule. The dyskeratosis, discovered incidentally, was localized in the mucosa of the hard palate, gums, cheeks and tongue. There were no cutaneous lesions. The coexistence of these two distinct diseases in the same region, the superior maxilla, suggests the possibility that they have a common origin, the assumption being that both are the expression of disordered embryonal development, such disorder being manifested through the action of endogenous or exogenous agents.

DENNIS, San Diego, Calif. [ARCH. OTOLARNG.]

PARROT'S PSEUDOPARALYSIS IN A PAIR OF TWINS OF THE SAME SEX. E. KUZNITZKY and ALICE KOPPEL, Dermatologica **81**:153 (March) 1940.

Female twins, born prematurely to a mother with latent and untreated syphilis, showed no signs or symptoms of syphilis at birth. In the third to fourth week mild febrile temperatures were noted. At the age of 6 weeks Parrot's pseudoparalysis appeared simultaneously in both twins, accompanied by coryza and strongly positive reactions of the blood serum. Uniovularity or binovularity of the twins was not determined.

THE QUESTION OF CONGENITAL TRANSMISSION OF LYMPHOGRANULOMA VENEREUM. N. MELCZER and K. SIPOS, Dermatologica **81**:163 (March) 1940.

The authors report the case of a 39 year old woman with genitoanorectal elephantiasis due to lymphogranuloma venereum. Already suffering from this disease, she had given birth to a girl, who at the age of 3 years had repeatedly positive reactions to Frei tests but no signs of a past or present infection with lymphogranuloma venereum. This allergy of the child was regarded as the result

of a healed infection. Five months later five tests with different human Frei antigens gave repeatedly completely negative results. Retrospectively, the previous positive results of the tests were considered nonspecific.

H. O. CURTH, New York.

A RE-EXAMINATION OF CASES OF FRESH SYPHILIS TREATED IN 1912-1913. (PRELIMINARY REPORT). GUNNO WILLNERS, Acta dermat.-venereol. **20**:463 (Aug.) 1939.

Of 616 patients treated and reexamined after twenty-five years, about one fifth of the number had died, three fifths were still alive, and one fifth could not be traced. In 11 of those who died (1.78 per cent) death could be attributed to syphilis. In these the interval between infection and death varied from eight to twenty-two years. One hundred and twenty-one patients (19.64 per cent) were symptom free. The treatment of most of these patients, if any treatment at all was undertaken, consisted of the intermittent use of mercury. A comparison of the death rate among this group of syphilitic persons with that of the general population revealed a 32 per cent higher death rate for the syphilitic group.

CONTRIBUTION TO THE KNOWLEDGE OF THE PROGNOSIS OF SYPHILIS WITH REFERENCE TO LATE COMPLICATIONS IN THE CARDIOVASCULAR SYSTEM. M. TOTTIE, Acta dermat.-venereol. **20**:471 (Aug.) 1939.

The cardiovascular system of 264 patients with syphilis of more than eight years' duration was studied. Among 141 patients who were found to have aortitis only 1.4 per cent had been adequately treated and only 4.2 per cent had received injections of arsphenamine. None of the adequately treated patients had decided aortic changes. The author concludes that the administration of arsphenamine not only does not increase the frequency of vascular syphilis and neurosyphilis but actively protects a person infected with syphilis against the development of complications.

THE PROGNOSIS OF TREATED SYPHILIS. ESBERN LOMHOLT, Acta dermat.-venereol. **20**:482 (Aug.) 1939.

The prognosis of syphilis in regard to the development of late involvement of the central nervous system is discussed. The author stresses the necessity of spinal puncture and advises that it should be performed not immediately after the conclusion of treatment but one year later. According to the author's experience, neurosyphilis will not develop if the patient is symptom free and if the spinal fluid is found to be normal one year after the conclusion of antisyphilitic treatment. Only one exception to this rule was found in the literature. On the basis of his experiences in the Rigshospital, the author states the belief that in about 10 per cent of the syphilitic patients who have been treated for early syphilis within the period of 1911 to 1920 general paralysis will probably develop.

A CASE OF MELANOSIS AFTER SALVARSAN [ARSPHENAMINE] DERMATITIS. MARTIN RUBNER, Acta dermat.-venereol. **20**:502 (Aug.) 1939.

The author describes a case in which melanosis developed following generalized exfoliative dermatitis due to arsphenamine. The skin was gray-black. In time regrowth of hair and nails took place, but the melanosis remained. The administration of ascorbic acid for three weeks did not change the melanosis.

ANOGENITAL ULCERATIONS ON AN EMBOLIC BASE. S. HELLERSTRÖM, Acta dermat.-venereol. **20**:514 (Aug.) 1939.

The author discusses nonvenereal anogenital ulcerations and cites 3 cases in which the ulcerations were situated on a base which was embolic in appearance. Each of these patients (women) was suffering from some form of cardiovascular disease. Two of them also presented similar ulcerations on the nose or in the

groin. The general aspect of the ulcerations was similar to that of necrosis following electrocoagulation, and the process was sluggish and refractory to any treatment. The author considers these ulcerations as some form of vasculocirculatory necrosis, and his conception was supported histologically by the presence of vascular changes. The author discusses fully the differential diagnosis and comes to the conclusion that these ulcerations are formed on an embolic-thrombotic base in patients suffering from cardiovascular disturbances. Trauma and the presence of microbial flora in the anogenital region may be contributing factors in the formation of these ulcerations. The prognosis and treatment are discussed.

ASTRACHAN, New York.

MONOCYTIC LEUKEMIA. P. PLUM and S. THOMSEN, Ugesk. f. læger **100**:755 (July 7) 1938.

A boy of 11 years became ill with a high fever and an eruption of scanty large vesicular efflorescences. At examination he was found to have also enlargement of the lymph nodes of the neck. The liver and spleen were not palpable. The blood culture was sterile. The hemoglobin content was 66 per cent. The white blood cell count was 525, with 15 per cent granulocytes (3 per cent segmented), 49 per cent lymphocytes, 9 per cent monocytes and 27 per cent unclassified mononuclear leukocytes. The latter cells were of the same size as the monocytes but had more basophilic cytoplasm. The nucleus was globoid and contained up to four nucleoli.

The bullous eruption progressed and finally involved most of the skin. The new vesicles were hemorrhagic. At the slightest trauma of the skin the epidermis was loosened. The white blood cell count increased to 30,000, with an increase in the number of large monocytic cells (90 per cent). The liver, spleen and lymph nodes showed clinically no changes. The fever continued. The boy died ten days after the beginning of the disease.

Postmortem examination showed hyperplasia of the lymph nodes, spleen and bone marrow, degeneration of the liver and kidneys, and bronchopneumonia. Microscopic examination revealed monocytic pneumonia, large agglomerations of monocytic cells in the skin and abundant monocytes of various sizes in the bone marrow. There was no infiltration of the liver and spleen.

WALLGREN, Göteborg, Sweden. [AM. J. DIS. CHILD.]

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

E. William Abramowitz, M.D., *Chairman*

Lewis B. Robinson, M.D., *Secretary*

March 5, 1940

A Case for Diagnosis (Dermatitis Medicamentosa [Acetylsalicylic Acid]?).
Presented by Dr. E. William Abramowitz.

M. L., a woman aged 32, presented from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, gives a history of having had an eruption similar to the present one four years ago after taking acetylsalicylic acid. She is sure that she took no other drug at that time. The eruption persisted for a long time, leaving brownish pigmentation which lasted for almost a year. The present eruption is of two and one-half weeks' duration and appeared within twenty-four hours after ingestion of a 5 grain (0.32 Gm.) tablet of acetylsalicylic acid and 2 tablespoonfuls of magnesia magma. She complains of itching and burning. No history of the ingestion of any other drug can be obtained. The lesions vary in size and are erythematous and edematous. They are located on the upper extremities, the largest patches being on the elbows. There is one small patch on the outer side of the right leg.

DISCUSSION

Dr. Louis Chargin: The condition is apparently a drug eruption, but I doubt whether the eruption can be attributed to acetylsalicylic acid. Eruptions due to this drug are very uncommon, but when they do occur, I do not think they are of the erythema multiforme variety. I would rather attribute the eruption to phenolphthalein or to a drug of the phenobarbital group. The case should be investigated from the standpoint of these drugs as well as acetylsalicylic acid.

Dr. George C. Andrews: In spite of the large quantities of acetylsalicylic acid that are consumed, eruptions due to it are rare, but when they do occur I think they are described as the urticarial type, the erythema multiforme type or the angioneurotic edema type. This woman is positive that the cutaneous condition came from acetylsalicylic acid the first time and also the second time. She is so sure that she is willing after this eruption subsides to take more of the drug to prove the theory. I believe this eruption was due to the drug in question. The slate color of one patch on the wrist is typical of a drug eruption. .I had a case in which acetylsalicylic acid was definitely the cause of angioneurotic edema.

Dr. Charles Wolf: I agree with Dr. Andrews. I am of the opinion that this eruption is due to acetylsalicylic acid. It so happens that I have in the last ten days encountered 2 cases of drug eruption in which there was no question of any other drug having been ingested. One patient gave a history of having taken acetylsalicylic acid for eighteen years. She is in the employ of a physician in a domestic capacity in his home. He sent her to me within twenty-four hours after the eruption had appeared. On examination there were lesions of an urticarial, erythema multiforme and angioneurotic edema type. The other patient gave the same history of ingestion of the drug and presented the same type of eruption, urticarial and angioneurotic edema type, and also a flat circinate papular erythema multiforme type of eruption. The three types of eruption appeared simultaneously on different parts of the body.

DR. E. WILLIAM ABRAMOWITZ: I agree also with Dr. Andrews that the common type of eruption that appears from acetylsalicylic acid is usually the erythema multiforme type. Those who are subject to a specific type of hypersensitivity, such as asthma and hay fever, usually have this type of eruption. I have seen such a condition in a patient of Dr. Frank Fraser. She had several attacks and in the last one was quite ill. There have been a number of fatalities from acetylsalicylic acid in patients subject to a specific type of hypersensitivity. The other type of eruption from this drug is a dyshidrotic and eczematous eruption and occurs in persons apparently with no atopic history. The lesions usually affect the palms and soles and also the genitals. This patient will be carefully investigated and tested with acetylsalicylic acid and magnesia magma, as well as with other drugs and agents, to determine the exact cause of the eruption and the possible presence of polysensitivity. If the magnesia magma contained phenolphthalein, the solution would be red, as the former is alkaline. I am not aware of any magnesia magma that is not white.

A Case for Diagnosis (Eczema? Chronic Exudative Lichenoid Discoid Dermatosis?). Presented by DR. HENRY D. NILES.

B. B., a man aged 39, is presented from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, complaining of a generalized eruption which started in the summer of 1936 with generalized pruritus. No eruption was present at that time, but within six months generalized erythroderma developed, followed by exfoliating dermatitis. In November 1937 symptoms suggestive of peripheral neuritis developed, for which he was admitted to the New York Neurological Institute on November 12. A diagnosis of acute multiple neuritis, cause undetermined, was made. Treatment consisted of repeated spinal punctures for drainage and administration of vitamin B_1 intravenously and by mouth. He was discharged from the hospital on Jan. 8, 1938, as improved in the status of both the cutaneous condition and the neurologic condition. He returned to work and remained fairly well until November 1939, when he was admitted to the New York Post-Graduate Medical School and Hospital with exfoliative dermatitis. While he was in the hospital numerous erythematous edematous discoid lesions developed on the trunk and on the extremities. He was discharged as improved on Jan. 5, 1940. The patient was never free from lesions, and on February 25 he was again admitted to the hospital with bright red coin-sized edematous discoid lesions over the trunk, face and extremities. Lesions were also present on the shaft of the penis. On retrogressing, the lesions showed a heavy scaling.

Physical examination showed essentially no abnormalities except the cutaneous condition and chronic purulent otitis media on the left side.

Repeated Wassermann tests of the blood gave negative reactions. The Wassermann reaction of the spinal fluid was also negative. On Jan. 8, 1938 examination of the spinal fluid showed 2 cells per cubic millimeter, a 2 plus reaction for globulin and 100 mg. of protein per hundred cubic centimeters. The colloidal gold curve was normal. Chemical examination of the blood showed 4.5 mg. of uric acid per hundred cubic centimeters; all other readings were within normal limits. Repeated blood counts were normal except for 17 per cent eosinophils. Examination of the urine for arsenic on Nov. 29, 1939 showed arsenic as arsenic trioxide, 0.1 mg. per hundred cubic centimeters, or a total of 0.97 mg. Another examination on March 1, 1940 showed 0.01 mg. per hundred cubic centimeters, or a total of 0.11 mg.

The histologic diagnosis on Dec. 21, 1939 was eczematoid dermatitis. A second biopsy specimen was taken on Feb. 28, 1940, and the histologic diagnosis was reticuloendotheliosis, possible mycosis fungoides.

DISCUSSION

DR. DAVID L. SATENSTEIN (by invitation): I think that the diagnosis of reticuloendotheliosis should not be taken seriously. I saw that slide this afternoon. In other cases of this type there has been an opportunity to examine sections at

various stages of the disease. In some cases the clinical picture was not that of mycosis fungoides and yet the histologic changes were those of mycosis fungoides. In others the clinical picture was of mycosis fungoides, and microscopically there was only simple inflammation. With this disease the microscopic picture may vary from week to week.

DR. MARION B. SULZBERGER: It is difficult to make a diagnosis in such a case on just one inspection. However, certainly the condition is not eczema, and I suspect that it might well belong in the group of dermatoses which Dr. Garbe and I described in detail (Sulzberger, M. B., and Garbe, W.: Nine Cases of a Distinctive Exudative Discoid and Lichenoid Chronic Dermatosis, ARCH. DERMAT. & SYPH. **36**:247 [Aug.] 1937), cases of which have been presented here repeatedly and discussed, particularly by Dr. Rosen and others. Before giving a decision, I should like to know more about this case. Have there ever been rapid remissions on a change of environment? If so, this fact would be in favor of the diagnosis mentioned. I think that the fact that conditions of this sort so often improve with changes in environment, together with the fact that many cases of them have been followed for so many years without the condition eventuating in a blood dyscrasia, mycosis fungoides or any of the so-called lymphoblastoma group of dermatoses, is in favor of the condition's being a separate entity. I think the fact that this disease occurs preponderantly, if not exclusively, in males also speaks strongly against its lymphoblastomatous nature. As far as I know, lymphoblastomas do not have this predilection for one sex.

One point I should like to mention is that foci of infection have been found in some cases of this type. I do not mean the ordinary hidden foci of infection which one could probably find in any adult if one looked hard enough; I mean the apparent, active foci of infection. One case I recall was that of a man with ordinary paronychia of the finger, which persisted for many months in spite of conservative therapy. Not until I evulsed the nail was the focus cured, and then the dermatosis, too, cleared up in a short time. Several of my patients had such foci of infection. Dr. Niles's patient has such a focus in the left middle ear. I think it would be interesting to see what would happen to the dermatosis if one made every effort to clear up the particular focus of infection in this case.

DR. HENRY D. NILES: I was glad to hear Dr. Sulzberger's discussion, because in making this diagnosis I felt that this case would probably fall into the group which he described. The patient is of the right race and of the right temperament, being neurotic. His eruption is of long duration and has had a varied clinical picture. On the first admission there was an exfoliative dermatitis, and the discoid lesions were more or less masked by the universal eruption. When he first came in on his second admission, the lesions were a much brighter, bluish red and suggested a drug eruption, but I could obtain no history of the ingestion of any drug except magnesia magma. He has improved during this stay in the hospital, although he has been there only a short time.

DR. E. WILLIAM ABRAMOWITZ: What is the relation of the peripheral neuritis which this patient had to the arsenic studies or the cutaneous condition?

DR. HENRY D. NILES: I believe the peripheral neuritis was due to a vitamin B deficiency. He was given a high vitamin diet on his first admission, although he had no neuritis when I first saw him.

Erythroderma Ichthyosiforme Congénitale. Presented by DR. ADOLPH ROSTENBERG.

A. B., a woman aged 19, was previously presented before the Bronx Dermatological Society on Feb. 29, 1940 (ARCH. DERMAT. & SYPH. **42**:527 [Sept.] 1940).

DISCUSSION

DR. MAX SCHEER: The erythema of the face, the so-called red Indian face, the general erythroderma and hyperkeratoses of the palms, in spite of the fact that the lesions are not so evident on the flexor aspects, all make this case in my opinion a typical one of congenital ichthyosiform erythroderma.

DR. DAVID BLOOM: I am not ready to accept with conviction the diagnosis given, because the observations in this case do not agree in many points with the description given of this condition, particularly the lack of involvement of the flexor aspects of the joint.

DR. LEWIS B. ROBINSON: I think this case is as typical a one of congenital ichthyosiform erythroderma as I have encountered. I recommend reading the excellent article by Dr. Rosen and Dr. MacKee (Rosen, I., and MacKee, G. M.: *J. Cutan. Dis.* **35**:235 [April]; 343 [May-June]; 511 [Aug.] 1917).

DR. DAVID L. SATENSTEIN: Concerning the rigidity of the criteria for making a diagnosis in these cases, when an observer reports a few cases with his observations, I am certain that the next few cases that are reported of a similar condition will show some new variations. There are few cases which will compare exactly in every detail with the case which the writer originally described. The case presented tonight is an example of this.

DR. DAVID BLOOM: I believe that it is logical to request that a disease to which a certain name is given should conform to the descriptive features given by the author who originated this name. If it does not, another name should be used.

DR. LEWIS B. ROBINSON: I believe that this case fits absolutely what was described by Rosen and MacKee.

DR. ADOLPH ROSTENBERG: This condition was described by Brocq (Brocq, L.: Erythrodermie congenitale ichthyosiforme avec hyperdermoatrophie, *Ann. de dermat. et syph.* **33**:131, 1902) as an entity. He took it out of the generalized group of ichthyosis and gave it the name mentioned. The condition in this case conforms to everything which the name implies. There is erythroderma; there is ichthyosis, and there is a congenital onset. It is unnecessary to split hairs about the congenital aspect of the condition just because the mother says she noticed the condition when the child was 2 years of age. There are cases on record in which the condition was not noticed until the age of 6 years or even later. Therefore, every requirement of erythroderma ichthyosiforme congenitale is fulfilled in this case with one exception. In most of the cases reported, and there have not been many, the majority of the ichthyotic lesions have been seen on the flexor surfaces, while in this case they are mostly on the extensor surfaces. The first feature one notices in this case is the pronounced erythroderma. There is no case of ordinary ichthyosis on record in which there is pronounced erythroderma.

Amyloidosis Cutis (Localized). Presented by DR. E. WILLIAM ABRAMOWITZ.

I. R., a man aged 54, is presented from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, complaining of an eruption involving the lower extremities and buttocks of three years' duration. Examination shows grouped papular lesions on the flanks and buttocks. The extensor surfaces of both legs are almost completely covered by numerous discrete, pinpoint-sized to pinhead-sized, yellowish brown, infiltrated papules.

The Wassermann and Kahn reactions were negative. A blood count showed 86.4 per cent hemoglobin, 4,300,000 erythrocytes and 7,950 leukocytes per cubic millimeter and a differential count of 56 per cent polymorphonuclear leukocytes, 37 per cent lymphocytes, 4 per cent monocytes and 3 per cent eosinophils. The chemical examination of the blood showed 55 mg. of sugar per hundred cubic centimeters. Histologic examination showed amyloidosis.

A 1 per cent solution of congo red was injected subcutaneously into the site of the lesions on the leg and caused the development of a reddish pink color, which persisted for some time.

DISCUSSION

DR. MAX SCHEER: From the clinical standpoint alone, all one can see is that the man has neurodermatitis.

DR. GEORGE C. ANDREWS: I do not agree with Dr. Scheer. I admit that it is difficult to see any lesions in this case characteristic of amyloidosis, but there is a small area on the outer side of the left shin, a few inches long, of which the

color and waxy, glazed appearance are to my mind characteristic of amyloidosis. That diagnosis is a fairly definite one, particularly since it has been confirmed by histologic examination.

DR. DAVID L. SATENSTEIN: I have had some sections in times gone by in which the presence of amyloid in the tissues could easily be demonstrated. I had an interesting case this week. The tentative clinical diagnosis was amyloidosis. Two pieces of tissue were sent in, one in solution of formaldehyde and the other in the routine fixative. Paraffin sections were made and stained and found to be normal. Frozen sections stained with methyl violet were also made and were the most beautiful sections that I have ever seen. Therefore, I say that in cases of this kind it is not wise to rely on the paraffin sections alone.

As far as the clinical aspect of the case is concerned, the original description is given as a papular lichenoid eruption of the skin of the legs which may be brownish and which is pruritic, persistent and resistant to therapy. The patient has had this condition for three and one-half years. In that time changes have taken place, and the original picture has changed. The eruption became flattened. Must the diagnosis be discarded because the clinical picture does not conform to the orlginal description of this condition, even though it has been confirmed microscopically?

DR. HENRY D. NILES: What treatment has this patient had in the last two weeks? He was presented at the staff conference at the Skin and Cancer Unit two weeks ago. Either the light was better on that occasion than it was tonight or something else was different, because it seemed to me that then the lesions on his legs were typical of amyloidosis, much more so than now, and also he had a much more extensive eruption on the trunk than he has at present. At that time there were small excoriated papules like prurigo on the trunk, which have now mostly disappeared.

DR. E. WILLIAM ABRAMOWITZ: I was not certain that this man had amyloidosis, especially in view of the fact that he had a considerable number of pruriginous lesions on the trunk. However, on looking closely at the lichenified areas on the legs I saw what I thought were waxy papules, and I thought he might have two conditions, neurodermatitis and amyloidosis. I was not surprised at the histologic report of amyloidosis, because the local injection of congo red also gave a positive reaction. The patient has had no treatment, and although the eruption has improved somewhat on the body, he complains bitterly now of the intense itching of the legs. In another case, mentioned by Dr. Satenstein, the itching was reduced with about twelve weekly treatments with unfiltered roentgen rays of about 75 r each. The appearance of the lesions did not change much.

E. WILLIAM ABRAMOWITZ, M.D., *Chairman*

LEWIS B. ROBINSON, M.D., *Secretary*

April 2, 1940

Ulcer of the Leg. Presented by DR. A. BENSON CANNON.

W. R., an Irishman aged 68, was admitted to the City Hospital in 1928 with an ulcer of the leg which had been present for one year. A previous ulcer at the same location had healed after three years of treatment and had remained healed for one year. The past history was irrelevant except for a compound fracture of the left leg at the site of the present ulcer. There was no history of syphilis or of treatment for syphilis. The patient never noticed any varicose veins in either leg. While he was in the hospital all forms of treatment for the ulcer of the leg were used, without permanent success.

Examination shows multiple ulcerations varying from 2 by 1.5 cm. to 8 by 6 cm. in size, irregular in shape, sharply defined, with elevated rolled, beveled edges and superficial necrotic, yellowish bases. They involve the entire left leg

from below the knee to the ankle, particularly the anterior and lateral surfaces. The ulcerations are situated in boardlike, scarred, red skin. Most of the soft parts are destroyed from the ankle to the middle third of the leg on the anterolateral surface, leaving exposed bone in one place. The foot is somewhat swollen. There are no varicosities in either leg.

Roentgenograms of the leg show changes in the cortex of the left tibia and fibula, with productive periosteal changes. These changes are not characteristic of osteomyelitis but rather suggest changes secondary to soft tissue involvement, such as one sees in varicose ulcers. The blood count and urine were normal, and the Wassermann reaction of the blood was negative.

DISCUSSION

DR. GEORGE C. ANDREWS: I think that antisyphilitic treatment ought to be tried.

DR. HERMAN GOODMAN: Years ago there were many ulcers of the leg in the clinics, and the youngest man on the staff had to dress them. Records were kept of such ulcers at Bellevue Hospital, Hudson Street Hospital and some other institutions in lower New York. Of several hundred patients who presented ulcers of one leg alone, ulcer of the left leg occurred only once out of three times in patients with syphilis, as compared with ulcer of the right leg, which occurred two out of three times. A study made later indicated that this should be so on anatomic grounds. The left leg is subject to stasis more than the right leg. According to the anatomy of the lower part of the abdomen, there is the added weight of the bowel on the right side, and the crossing of the veins returning the circulation from the lower part of the leg to the vena cava close to the artery are on the right side also. Studies on the cadaver disclose that the remnants of the fetal vein exist on the left side and not on the right (Goodman, H.: Ulcer of the Leg, ARCH. DERMAT. & SYPH. **6**:179 [Aug.] 1922). Mention is now made because of the reference to antisyphilitic therapy in a person who has an ulcer on the left leg only. The treatment in the old days consisted in cleaning the wound and removing maggots. Then it was advised that maggots healed ulcers of the leg. One can now purchase an extract of maggots and apply it to the ulcers, with therapeutic results which no other form of therapy gives. If the roentgenogram shows bone change, the condition would not be affected by superficial therapy alone.

DR. A. BENSON CANNON: I thought that this man presented a typical example of extensive traumatic ulcerations of the leg with arteriosclerosis. I considered the ulcerations characteristic of ulcers of the leg; besides, they are situated in the hard, sclerotic, pigmented skin. The location, the character of the lesions, the changes in the surrounding skin and the persistently negative reactions to Wassermann and precipitation tests leave little doubt that this condition is not due to syphilis. From 45 to 65 patients with ulcers of the leg are under observation at the City Hospital continuously, and it is not uncommon to encounter arteriosclerotic ulcerations of this character in elderly people. There is nearly always associated periostitis and osteitis, the fibula being more involved than the other parts. While this man's ulcer has been healed on several occasions, he has returned in a few months with a recurrence. Probably the only permanent cure in this case would be amputation of the extremity. His age and physical debility make him a poor surgical risk.

Eczema (Due to Quinine?). Presented by DR. GEORGE M. LEWIS.

R. C., a housewife aged 37, is presented from New York Hospital for Dr. Lionel C. Rubin. Since September 1939 she has had four outbreaks of an eruption on the backs of the hands and on the face. There is a history of her taking "rhinitis tablets" (containing camphor, belladonna and quinine). A week ago a new type of eruption appeared on scattered areas of the arms and legs. She has not recently taken any medicine.

When the patient was examined on February 20, there were large bullous lesions on the left cheek and on the backs of both hands. There was a purplish brown halo around these lesions. The patient also had asymptomatic tinea pedis.

She was given 0.5 Gm. of phenolphthalein, which caused no exacerbation. On February 27 she took two "rhinitis tablets," with an exacerbation following within a few hours. One grain (0.06 Gm.) of quinine was taken on March 6, with a definite exacerbation of the eruption on the backs of the hands, consisting of increased redness, scaling and vesiculation. On March 24, new coin-sized patches of scaling, erythema and vesiculation appeared on the arms and on the left ankle.

The Wassermann reaction was negative. Examination for fungi gave negative results. The trichophytin and oidiomycin tests gave positive results.

DISCUSSION

DR. E. WILLIAM ABRAMOWITZ: The usual type of eruption from the internal use of quinine is scarlatiniform erythema; an eczematous eruption is usually due to contact. I saw a patient in whom dermatitis developed first on the face from the use of eau de quinine. Two years later severe dermatitis of the genitals developed, with dissemination of the eruption on the body, which was of the macular erythema multiforme type. The history I obtained was that the eruption appeared right after sexual intercourse. His wife used a contraceptive jelly containing oxyquinoline sulfate. Although no tests were carried out, the story was consistent with the development of the eruption. The man was in the hospital because the eruption was so severe. An eczematous eruption may appear from the internal use of a drug after contact dermatitis has occurred from the same drug.

DR. RICHARD J. KELLY: I should like to ask Dr. Abramowitz if he has seen any eruption in his experience like this caused by a drug.

DR. E. WILLIAM ABRAMOWITZ: I have also had experience with sensitization to oxyquinoline sulfate in a chemist who prepared oxyquinoline sulfate tablets. In preparing them he dropped some of the drug on his foot. It went through his shoe, and dermatitis of the feet developed from it.

DR. PAUL GROSS: This case brings out the fundamental problem of drug eruption. The patient presents an eczematous eruption, and it is suggested that the cause may be quinine, which the patient has taken by mouth. The interpretation of an eczematoid dermatitis as a drug eruption cannot be accepted without absolute proof. So far, all evidence suggests that such eruptions are based exclusively on the mechanism of sensitization from without to within. As an example, I may mention a case in which a man had an acute contact type of dermatitis of the face and neck, suggesting one due to a hair lotion or hair dye. Careful questioning revealed that the patient had a similar eruption one-half year before which was traced to quinine hair lotion, but he stated that he had not used any application to the hair and face recently. Further investigation brought out the following facts: A day before the onset of the eruption, the patient had visited a friend whose wife was in ill health. She had been given a tonic but refused to take it because of its bitter taste. To encourage her, both men took a spoonful of the tonic (iron, quinine and strychnine). The second eruption brought about by the intake of quinine was confined to the areas previously affected by the contact dermatitis. Of course, every dermatologist has had similar experiences illustrating this sensitization. Even for arsphenamine dermatitis the sensitizing effect of the unavoidable intradermal contact with the solution attached to the needle has been brought forward as explanation.

DR. GEORGE C. ANDREWS: I have observed several instances of extensive dermatitis in babies on whom an oil containing oxyquinoline sulfate has been used.

DR. E. WILLIAM ABRAMOWITZ: I know of no proved factors that will bring on sensitization to drugs. Stokes believes that foci of infection may be responsible. A person sensitive to one drug may become sensitized to several drugs.

DR. TIMOTHY J. RIORDAN: A Swedish man was in the habit of taking gin tonic, a long drink containing gin in a beverage of quinine water. This was readily available in Sweden, but he could not procure it here. He had a chemist make up some quinine water as a substitute. He took this for a while, and then erythema multiforme or a maculopapular type of eruption developed on the face and wherever he perspired, as in the axillary and pubic regions.

DR. GEORGE M. LEWIS: It is not certain that quinine is the sole cause of the eczema in this patient, but it surely caused an exacerbation and plays a role in the causation. It is possible that sensitization to quinine has predisposed the patient to sensitivity to other allergens. Eczematous lesions now seem to be developing with no relation to the ingestion of quinine.

DR. HERMAN GOODMAN: This woman may have applied sunburn preventive cream or lotion. Some of them contain up to 5 per cent quinine, included on the basis of the theory that fluorescence protects from the effects of the sun.

Dermatitis Medicamentosa; Fixed Eruption (Due to Mapharsen). Presented by DR. GEORGE M. LEWIS.

A. C., an unmarried Negress aged 22, was admitted to New York Hospital on Oct. 13, 1939, with a maculopapular syphilid. The Wassermann reaction was 4 plus. She received combined treatment with mapharsen and a bismuth compound. There was some pruritus following the second injection of mapharsen, but when the dose was reduced there were no further symptoms. From October 14 to December 15, sixteen injections of mapharsen and four injections of a bismuth compound were given. The latter injections were then followed by resumption of therapy with mapharsen. Following the second injection of mapharsen an eruption appeared on the trunk. No arsenical compound has been given since Feb. 8, 1940. There is no pruritus. She does not take laxatives or any other medicine.

Examination shows several discrete, oval and rounded, flat, deeply pigmented plaques on the trunk and neck. There is no evidence of scratching. There is slight scaling.

The histologic observations were as follows: The increase in pigmentation could be explained by the patient's race. There were fibrosis of the corium and much perivascular infiltration. The infiltrate consisted chiefly of lymphocytes, although a few polymorphonuclear leukocytes were present, and many of the endothelial cells were swollen and appeared large and pale staining.

DISCUSSION

DR. A. BENSON CANNON: I think the term lichenoid eruption following treatment with mapharsen a better or more appropriate designation than fixed eruption. The plaques are certainly lichenoid and scaly and are not sharply demarcated, as are fixed eruptions.

DR. FRANK VERO: I presented here about three years ago the first case of fixed eruption due to mapharsen in a Negress (Fixed Eruption Due to Arsenic, ARCH. DERMAT. & SYPH. **35**:307 [Feb.] 1937). However, she also gave a history of a fixed eruption after the use of neoarsphenamine and silver arsphenamine. Pigmentation occurred without any previous inflammatory changes. There were no infiltrations or scaling. I, too, feel that the case presented is not one of typical fixed eruption.

DR. E. WILLIAM ABRAMOWITZ: Have fixed eruptions occurred as a result of the four day plan of treatment with arsenicals?

DR. LOUIS CHARGIN: I have seen no fixed eruptions from that treatment.

DR. E. WILLIAM ABRAMOWITZ: My impression is that it is more of a pityriasis-rosea-like eruption which this patient presents, and whether it is due to mapharsen or to bismuth still has to be determined. The patient showed definite wrinkled lesions, and there is entirely too much color there now for the eruption to have been present almost two months. I am willing to accept it as a fixed drug eruption if the administration of mapharsen causes it to flare up.

DR. GEORGE M. LEWIS: This patient is obtaining her antisyphilitic treatment somewhat surreptitiously and is concerned with the possibility that this eruption will appear on her face. The question of the advisability of further arsenical therapy and whether to continue with mapharsen or to change to old arsphenamine were given some thought. I do not believe there is any danger of exfoliative dermatitis. I am glad that Dr. Abramowitz agreed that the appearance of these lesions is compatible with the diagnosis of fixed eruption.

Dermatitis Herpetiformis (Treated with Sulfanilamide); Arsenical Keratoses. Presented by DR. GEORGE M. LEWIS.

T. W., a man aged 53, a milk salesman, is presented from New York Hospital, complaining of an eruption on the trunk, arms and scalp of five years' duration and an eruption on the palms of two years' duration. An eruption first developed five years ago, and he received various kinds of treatment, including repeated courses of arsenic internally, without any favorable effect. Pruritus has been severe. His personal history and family history are irrelevant.

Examination shows a grouped, vesicular eruption involving scattered areas of the trunk, shoulders, arms and scalp. The lesions are present on an erythematous base and are roughly symmetric. Numerous scratch marks are to be seen. There are areas of hyperpigmentation and depigmentation. The palms show small discrete keratoses.

The histologic picture is consistent with the diagnosis of Duhring's disease. The Wassermann reaction was negative.

The patient has received sulfanilamide, 5 grains (0.32 Gm.) three times a day, since Feb. 26, 1940, with substantial improvement.

DISCUSSION

DR. E. WILLIAM ABRAMOWITZ: I have 3 patients that have shown rather dramatic improvement with sulfanilamide.

DR. B. F. FELDEN (by invitation): I think one should be cautious in becoming overenthusiastic about improvement in a condition which is subject to spontaneous remissions, as Duhring's disease is. This patient has been treated with sulfanilamide since February 27, which means a little over four and one-half weeks. I had in my practice a patient with Duhring's disease whom I treated with azosulfamide (disodium 4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxynaphthalene-3', 6'-disulfonate); the patient had been under my care for over a year. I too found decided improvement with this treatment and was hopeful of getting definite results, but soon after the discontinuance of the medication, a prompt relapse occurred. On the second attempt to influence the condition with azosulfamide or sulfanilamide, there was no improvement at all. I should like to know if any one who has treated patients with Duhring's disease with sulfanilamide can really testify to a more permanent result, because a cure of four to six weeks' duration has no convincing significance with this disease, which lasts for many years or even a lifetime and which often shows spontaneous remissions for even four to six months, or longer, only to recur later.

DR. HENRY D. NILES: I think that one of the most interesting features in the history is the fact that the patient said the eruption improved remarkably in the first few weeks; then, even while the therapy was continued, it became worse and then improved again, which is unusual. I have had no such fortunate experience with sulfanilamide. I have treated several patients with dermatitis herpetiformis with sulfanilamide, with no good results at all. My experience with sulfapyridine has not been much better. I agree with Dr. Felden that the course of dermatitis herpetiformis is so capricious that there is great difficulty in evaluating the effects of any therapy. It undergoes regression with many forms of treatment, such as administration of sodium arsenate or of chromium sulfate and even injection of whole blood. When the stage arrives at which there is no more improvement, if another form of treatment is tried there may be successful results with that, too, at first. Then the patient becomes used to this, or something else happens, and there is no more benefit. I feel that sulfanilamide is such a potentially dangerous drug and dermatitis herpetiformis is such a relatively innocuous disease that one is not really justified in using it for relief of this condition.

DR. E. WILLIAM ABRAMOWITZ: I should imagine that in a case of severe dermatitis herpetiformis relief from itching and absence of cutaneous lesions for even three or four weeks would be welcome. For instance, a patient I presented before the class at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, who had had this condition for fifteen or twenty years,

was in a terrific mental state. The itching stopped after he took sulfanilamide, and the lesions began to fade. He was happy, although when administration of the drug was discontinued, after a few weeks, he had a recurrence. It was given to him again. The patient must, of course, be watched. I did not use a large dose, only 5 grains every three to four hours. If sulfanilamide does not work or if the patient cannot tolerate it, one can try sulfapyridine or even sulfathiazole. I have tried various methods of treatment, such as autohemotherapy and the administration of chromium sulfate, but I have never seen a response as quick as these patients show to sulfanilamide.

DR. GEORGE M. LEWIS: In another patient with dermatitis herpetiformis, the condition responded satisfactorily and the patient has remained well for the past six months with short courses of sulfanilamide interspersed with rest periods. In the case under discussion the patient has had almost continuous itching for five years and has previously been unresponsive to many different types of therapy. If the relief is only for four or five weeks, it is still worth while. Sulfanilamide is a potentially dangerous drug, and the patient must be observed for reactions and side effects, but there is no reason for not using the drug.

Dermatophytosis (Tinea Corporis). Presented by DR. GEORGE M. LEWIS.

J. H., a man aged 31, a stockman in a department store, is presented from New York Hospital. He first noticed ringlike lesions on the forearms two years ago. Similar lesions appeared on the legs, and the finger nails became involved and began to crumble. He has had numerous types of treatment, without permanent effect.

Examination shows a widely disseminated eruption on the trunk, arms and feet. The affected skin is dull red and scaly and is present in solitary, aggregated and configurate areas. Small discrete lesions are present on the buttocks. The soles are red but not noticeably infiltrated. Several red scaly areas are present on the neck. The nails of the index and middle fingers of the left hand are normal; the remaining finger nails show opacity, crumbling and destruction of varying degrees.

The result of microscopic examination of scrapings from the arm, back, buttock and neck was positive. Cultures from these sites all showed Trichophyton purpureum. The result of an intradermal trichophytin test was 2 plus in fifteen minutes and negative in forty-eight hours and after one week. The Wassermann reaction was negative.

Various fungicides and keratolytics have been used locally. Roentgenotherapy of the finger nails was abandoned as unsuccessful.

DISCUSSION

DR. JESSE A. TOLMACH: I think Dr. Lewis is to be complimented for focusing attention on these T. purpureum infections. It is now known that eczema, neurodermatitis and psoriasis may be simulated by this infection. You may, perhaps, recall the case I presented last year (ARCH. DERMAT. & SYPH. **40**:1057 [Dec.] 1939), which a number of the members thought was one of Duhring's disease. Further studies in that case showed that the cutaneous eruption was caused by T. purpureum. Positive cultures were obtained from the lesions on the forehead, trunk, axillas and groins.

DR. E. WILLIAM ABRAMOWITZ: The patient called my attention to the fact that I had seen him before. I recall that he had ringed lesions which brought up the question of erythema centrifugum. Has any one any suggestions on treatment for Dr. Lewis? Have inhalations of ethyl iodide ever worked in any of these cases, as claimed by Dr. Swartz? Has the presenter ever tried it? These conditions are resistant to treatment.

DR. JESSE A. TOLMACH: In my case the greatest amount of improvement was obtained from the application of a 1 per cent solution of iodine.

DR. E. WILLIAM ABRAMOWITZ: In a case of this kind, in which there is such decided involvement of the nails, would it not help to remove that focus? Have you had any experience with that procedure?

DR. GEORGE M. LEWIS: The cure of infections caused by T. purpureum is one of the most difficult problems in dermatology. At times it is apparently almost impossible. The lesions on the glabrous skin are the easiest in which to get results. They often respond to the usual types of antiparasitic therapy. It is a different matter when the toe nails, finger nails, palms, soles and beard are affected. If these sites are involved, vigorous and prolonged treatment will be needed. Evulsion of one nail may be performed, but this procedure is not indicated when many nails are infected or if the skin of the same hand or foot is also involved. It is helpful to scrape the nails vigorously before medicinal applications are made. It is important to look for involvement in the early stages and start treatment before the disease has extended to involve more than one or two nails or more than one or two areas of the skin. As far as the ethyl iodide inhalation method is concerned, I used the type of therapy advocated by Swartz and Reilly (Swartz, J. H., and Reilly, M.: Inhalation of Ethyl Iodide in Fungous Infections, ARCH. DERMAT. & SYPH. **32**:551 [Oct.] 1935) in exact detail and with the good cooperation of 3 patients, but I was unable to verify his results.

A Case for Diagnosis (Schamberg's Disease? Pigmented Purpuric Lichenoid Dermatitis?). Presented by DR. FRANK VERO.

G. T., a man aged 34, born in the United States, is presented from the New York Polyclinic Medical School and Hospital, complaining of an eruption on the palmar surface of the right hand and the flexor surface of the right forearm, of one year's duration. The patient was first seen on January 3. He gave no history of any previous cutaneous or venereal disease. The condition began with small pinhead-sized, reddish brown puncta, which gradually became larger and spread to the present extent.

A case for diagnosis.

Physical examination has shown no abnormalites. On the flexor surface of the right wrist there are numerous pinhead-sized to pea-sized, irregularly distributed, grouped, brownish yellow, macular and papular, slightly scaly lesions. Several lesions show minute telangiectases. The lesions on the palm appear larger

than those on the wrist and are reddish violaceous, slightly infiltrated and similarly studded with numerous telangiectases. An oval shaped, atrophic lesion on the wrist followed self treatment with concentrated nitric acid solution.

Repeated Wassermann and Kahn tests gave negative results. The blood count was normal. Microscopic examination showed a portion of skin, apparently from the palmar surface of the hand, which presented some keratinization of the surface epithelium and a well defined stratum lucidum. There was some dilatation of the capillaries immediately beneath the epithelium and a well defined lymphocytic infiltration involving the upper layers of the corium and penetrating into the deeper tissues as a perivascular lymphocytic infiltration. There was no evidence of hemorrhagic sarcoma of Kaposi or of purpura annularis telangiectodes of Majocchi. Hemorrhagic pigmentation was present but insignificant. The lesion was compatible with one of syphilis. The histologic diagnosis was chronic dermatitis (syphilitic?).

DISCUSSION

DR. GEORGE C. ANDREWS: I remember a similar case I had several years ago of a petechial eruption which was due to quinine. I questioned this man tonight, and he says he has been taking bromoquinine regularly for years whenever he gets a cold and has taken a great deal of it this winter. I think that is important, although clinically the condition does resemble Schamberg's disease. However, it is possible that it might be due to quinine.

DR. HERMAN GOODMAN: The patient told me a different story. He is a chemist working in a laboratory. He may have placed the side of the hand on the laboratory table. The eruption in this case is on the side of the hand and extends along the wrist. It is easy to duplicate that location by pressure on the side of the hand and the adjacent part of the wrist by resting the hand on the table. Some chemicals on the laboratory bench may have caused a protein reaction leading to this discoloration and the other changes on his hand.

DR. E. WILLIAM ABRAMOWITZ: According to the history, this man at one time applied some concentrated nitric acid to the lesion in trying to rid himself of the eruption. I recall a man whom I was treating at the Skin and Cancer Unit for possible Schamberg's disease; I found out he was rubbing his shins with sandpaper to stop the itching.

DR. EUGENE F. TRAUB: There is a possibility that this condition is a dermatitis artefacta; this diagnosis may seem far fetched, but there was something about the eruption that looked artificial. I am not prepared to say how the patient could produce such a picture, unless the method of production was somewhat on the order of the suggestion made by Dr. Goodman. I at least think it advisable to study this possibility further.

DR. HENRY D. NILES: The two diseases suggested by the presenter do not often occur on the hand or arm. Of course, they are not seen often even on the legs, but I do not recall ever seeing either condition on the hand. Because of two or three lichenoid papules, some of which I thought were umbilicated and some atrophic, and in spite of the slight purpuric appearance, I thought lichen planus might be considered.

DR. FRANK VERO: This patient has been under my observation for the last three months and has puzzled me a great deal. Various diagnoses were considered at the clinical conferences. Syphilis was first thought of, and the histologic picture also suggested this diagnosis. However, repeated Wassermann and Kahn reactions were negative, and injections of neoarsphenamine and four intramuscular injections of bismuth subsalicylate did not produce any change in his condition. Other diagnoses suggested were Majocchi's disease, early Kaposi's sarcoma and even lichen planus. The slides have been seen by other pathologists, and the possibility of lichen planus was considered. The patient has had this condition for a year, and as far as I could find out he takes no drugs. As far as Dr. Goodman's suggestion is concerned, the patient has not been working now for some weeks, and one would expect some improvement after the pressure on the

hands ceased. The patient has been working as a chemist and has handled various chemicals, but we were unable to determine a causal relation to this eruption. It is interesting to note that after the taking of tissue for biopsy several new lesions appeared. I am still unwilling to make a positive diagnosis and will study the case further.

Syphilid of the Hand. Neurodermatitis of the Calf. Presented by Dr. J. LOWRY MILLER.

H. E. D., a man aged 48, is presented from Vanderbilt Clinic. The patient had a chancre twenty years ago, with a Wassermann reaction of the blood of 4 plus. He received six injections of neoarsphenamine, eight injections of a bismuth compound and six injections of mercury from his physician. Later, in 1930, he received two and one-half courses (twenty-five injections) of old arsphenamine and one course (ten injections) of a bismuth compound at Vanderbilt Clinic. His Wassermann reaction became negative in 1932 and was still negative in 1938. However, in March 1940 it was again positive (with alcoholic antigen, 3 plus, and with cholesterol antigen, 4 plus). Cisternal puncture in 1931 showed the spinal fluid to be normal.

The patient has been treated at Vanderbilt Clinic at various times since 1928 for different cutaneous diseases affecting the trunk but chiefly the hands, elbows and feet, diagnosed variously as generalized trichophytosis, neurodermatitis, lichen planus and drug eruptions. Two years ago there was a lichenified, papular area on the medial aspect and calf of the leg and a recurrence of the earlier eruption on the extensor surfaces of both elbows. Both of these eruptions were characterized by itching in the initial stages. The lesions were treated with a proprietary preparation containing arsenic and mercury and with roentgen rays. The itching ceased, but the lesions remained. For the past month, the patient has had a lesion the size of a silver dollar on the left palm.

In 1920 the Wassermann reaction of the blood was 4 +, according to the patient's own statement. The results of further Wassermann tests are as follows:

Date	Wassermann Reaction		Kahn Reaction
	Alcoholic Antigen	Cholesterol Antigen	
Oct. 27, 1930	++++	++++	++++++
Feb. 2, 1931	+	+++	++++
Dec. 21, 1931	—	—	+
Nov. 15, 1932	—	—	0.7
March 9, 1938	—	—	—
March 21, 1940	+++	++++	++++

Cisternal puncture on March 26, 1931 showed that the Wassermann reaction of the spinal fluid was negative with both antigens, and the colloidal gold curve was 1111110000. Chemical examination of the blood on Jan. 6, 1931 showed: 462.7 mg. of sodium chloride, 106 mg. of sugar, 11.8 mg. of urea nitrogen and 4.62 mg. of uric acid per hundred cubic centimeters and an icteric index of 9. On Oct. 27, 1930 culture of material from the fingers showed Monilia albicans.

Histologic examination of a specimen of skin showed a wide keratin layer. The granular layer was also wide except where the epidermis showed maximum pathologic changes. In this location slight parakeratosis occurred. The epidermis was edematous and showed moderate leukocytic infiltration. Acanthosis was present. The underlying corium was heavily infiltrated by numerous small mononuclear cells. This infiltration was superficial and sharply demarcated. There was also a deeper perivascular infiltration. Many of these deeper cells appeared to be plasmocytes. Although the picture suggested lichen planus, because of the

presence of plasmocytes and the positive Wassermann reaction, the lesion must be considered to be of syphilitic origin. The histologic diagnosis was syphilis.

DISCUSSION

DR. B. F. FELDEN (by invitation): From the clinical appearance of the lesion, I think that a diagnosis of tertiary syphilid can be excluded. Whether this lesion previous to treatment was different in appearance is another question, but to make a diagnosis of tertiary syphilis one would require a palpable infiltration, which was absolutely not perceptible tonight. I should therefore like to know whether this lesion previous to treatment had a definite, palpable hardening.

DR. GEORGE C. ANDREWS: The whole picture is confusing to me. The patient has a lesion on the dorsum of the left hand which does not look at all like syphilis. It looks like an eczematoid lesion. There is also one on the dorsum of the right hand which looks like eczema. The lesion on the left palm is probably syphilitic. The lesions on the left leg are called neurodermatitis but have also been called lichen planus. He states that he had an eruption due to some medicine he took some years ago. The medicine was a laxative called "olive pills." The doctors at the hospital made him stop taking the pills, and the eruption went away. He says that the spots at that time were something like the lesions he has on the hands now. He is now taking some kind of pink tablets for constipation. I do not know whether they have anything to do with the eruption or not, but I think they should be mentioned in the history. Certainly the lesions on the dorsal surfaces of the hands do not look like syphilis at all, whereas the lesion of the left palm is syphilitic, clinically and microscopically.

DR. A. BENSON CANNON: When this patient was seen at Vanderbilt Clinic a few days ago, I do not think there was a physician who did not accept the diagnosis of the palmar lesion as being typical of syphilis. The horseshoe-shaped outline, the infiltrated and nodular margins of dark red and the clear and slightly atrophic center of the configuration were typical. The lesions on the backs of the hands and on the body were considered eczematoid in type, probably the result of treatment.

DR. E. WILLIAM ABRAMOWITZ: The lesions on the backs of the hands might possibly be a drug eruption or some other eczematous lesion, but the lesion on the palm even now shows some infiltration, and unless there is a superimposed drug eruption on top of the syphilitic eruption, which is a possibility, I think that the lesion on the palm is syphilitic. Nevertheless, I think some further testing should be done to see how that lesion and the other lesions respond to a test dose of a suspected drug.

DR. J. LOWRY MILLER (by invitation): I felt justified in making a diagnosis of syphilid of the palm because of the recurrence of the positive Wassermann reaction, which had been negative for several years. The lesion on the palm was definitely infiltrated and had a definite serpiginous border. It improved with injections of a bismuth compound alone. The other eruption is obviously something different and could well be explained by a drug eruption. In regard to the form of laxative he is taking, he takes cascara sagrada rather irregularly. He took some thirty-six hours ago, and there has been no particular impression on the lesions and no evidence of an exacerbation.

Acrodermatitis Chronica Atrophicans. Presented by DR. ANDREW H. MONTGOMERY.

H. S., a man aged 63, born in Austria, retired clothes presser, is presented from the New York Polyclinic Medical School and Hospital. Cutaneous lesions were first noticed six or seven years ago on the dorsum of the right hand. At present the right hand and the right leg are affected. On the dorsum of the right hand is a pellagra-like erythematous patch which extends to the dorsum of the fingers. The skin is thinned, inelastic, crinkly and transparent. A similar condition is present on the right elbow and on the right knee, with some branny exfoliation.

The skin on the rest of the right leg is atrophic and transparent and on the foot almost cyanotic. The whole leg shows strikingly numerous fine tortuous veins. Both legs show varicosities, the internal saphenous veins and their tributaries being involved. Pigmented and atrophic patches are located at the sites of sclerosing injections, which were given about a year ago.

The left leg is but slightly involved by the atrophic process. Over the tibial area are the usual dappled pigmentations following an old varicose eczema. About the middle third of the medial side of the calf is a palm-sized infiltrated area caused by a deep thrombophlebitis. There is moderate edema of the left leg.

Urticaria Pigmentosa (Adult Type). Presented by Dr. George M. Lewis.

S. S., a housewife aged 41, is presented from New York Hospital, complaining of an eruption on the trunk and extremities of five years' duration. She was first observed in the general medical clinic three years ago, when she was treated for the relief of constipation and for transient daily attacks of itching. When she again came to the hospital two months ago the eruption was still present. She noticed that the pruritus was always worse after excitement, worry, eating fish and exposure to heat. The results of physical examination were essentially negative. She has attacks of nervousness, which may be followed by dizzy spells and vomiting. The basal metabolic rate, as determined by her own physician, was —14 per cent. When her skin became itchy, she noticed small elevations.

Examination shows numerous small, rounded and oval, brown macules scattered over the trunk and extremities. On rubbing, whealing occurs, with redness of the surrounding skin.

Cutaneous tests, done in the department of allergy, all gave essentially negative results. The Wassermann reaction was negative. The urine and the hemogram were normal. Histologic examination showed the epidermis to be atrophic and somewhat hyperkeratotic. The horny layer was flaked off into a lacework of shreds. The rete cones were disorganized, and the epidermis was pigmented throughout. There was less in the stratum granulosum, and naturally it was most concentrated in the basal layer. There were tiny masses of keratin scattered throughout the epidermis. In the cutis basophilic mast cells were present in large numbers.

Dermatitis Medicamentosa (Mapharsen). Presented by Dr. Frank Vero.

P. P., a man aged 48, born in Italy, is presented from the New York Polyclinic Medical School and Hospital, complaining of an eruption on the arms, back and abdomen of five weeks' duration. The patient was first seen on Dec. 7, 1938, with a penile ulcer which was diagnosed as primary syphilis. The dark field examination showed Spirochaeta pallida. The Wassermann and Kahn reactions were negative. The patient has been receiving antisyphilitic treatment since then, with alternating courses of neoarsphenamine and bismuth subsalicylate. During June 1939, while receiving neoarsphenamine, he noticed an eruption on the left leg. This was diagnosed as lichen planus. He received six fractional doses of unfiltered roentgen rays (75 r weekly), with great improvement in the condition. From Nov. 15 to Jan. 3, 1940 he was absent from the clinic. When he returned he was given a course of treatments with mapharsen, receiving eight intravenous injections of 0.06 Gm., and an itching eruption appeared on the arms, back and abdomen. There was no history of ingestion of any other drug or of any local medication.

On the flexor surfaces of the forearms he shows a symmetrically distributed, fairly sharply outlined, erythematous and follicular, papular eruption. On the abdomen, hips and lower part of the back, he has a similar eruption with dryness and scaling. On the left leg there are patches of lichen planus undergoing involution, with deep pigmentation.

The patient has received several injections of sodium thiosulfate and various local treatments, without much improvement in his condition.

MANHATTAN DERMATOLOGIC SOCIETY

GEORGE C. ANDREWS, M.D., *President*

ANTHONY C. CIPOLLARO, M.D., *Secretary*

March 12, 1940

Eczema Venenatum (Perfume). Presented by DR. DAVID BLOOM.

J. S., a man aged 56, complained of a generalized pruritic eruption of three months' duration. The skin of the trunk and of the extremities was erythematous and excoriated, and that of the axillas, groins, lower part of the abdomen, genitals and hands was particularly involved.

As the history of the patient revealed that he had been occupied for many years in a cosmetic laboratory preparing creams, and as the ingredients of these creams were suspected to be the cause of the dermatitis, the patient was advised to avoid contact with the laboratory products. With application of soothing lotions and fractional roentgen ray treatment (75 r, unfiltered, weekly) the condition gradually improved until three weeks ago, when a sudden exacerbation of the eruption took place, with severe pruritus, depriving the patient of his sleep. Questioning elicited that the patient did not follow advice strictly. He handled perfume which was incorporated in one of the creams, and it soaked through the cotton gloves which he believed would protect him against contact with the laboratory products. At this time close questioning revealed that the patient had been in the habit, during the past few years, of applying this perfume (jasmin) freely to his skin, particularly in the axillas and groins.

Patch tests were then performed with three creams; one contained 0.05 per cent perfume, another contained sulfur and salicylic acid, and a third contained juniper tar (oil of cade) and methyl salicylate (oil of wintergreen). A fourth patch test was made with the jasmine perfume alone. Of the creams, only the one containing perfume gave a positive reaction, producing an erythematovesicular eruption in an area about 8 inches (20 cm.) in diameter around the patch area. Following instructions to avoid any contact with the perfume, the patient made a rapid recovery.

In order to analyze further the ingredients of the perfume responsible for the dermatitis, twenty-seven hours prior to this presentation patch tests were made (1) with benzylidene acetone (which is added by the manufacturer to the jasmine perfume for the purpose of intensifying its odor), (2) with perfume without benzylidene acetone, (3) with a better grade of jasmine perfume and, finally, (4) with the jasmine perfume which contains the benzylidene acetone. Two minutes after applying a solution of 1 crystal of benzylidene acetone in 1 cc. of water the patient complained of a severe burning sensation, and the patch had to be removed. Four hours previous to this presentation the results of the tests were read, and were as follows: 1. The area tested with the strong concentration of benzylidene acetone showed still an erythematous reaction, although the patch had been in contact with the skin for only two minutes. 2. The area tested with a solution of a crystal of benzylidene acetone in 35 cc. of water showed a bullous reaction. 3. The patch test with the regular jasmine perfume used by the patient in his laboratory and containing benzylidene acetone also caused a bullous reaction, although less intense. The skin around these three patches was erythematous and covered with small vesicles. 4. The patch test with the perfume not containing the benzylidene acetone did not cause a definite reaction. 5. The test with the better grade of jasmine perfume did not give a definite reaction. However, the skin around the last two patches was erythematous and covered with tiny vesicles, although the reaction was much less intense than that around the first three patches.

DISCUSSION

DR. HERMAN SHARLIT: It is interesting in cases like this to find out how long the patient is exposed to the irritant before he reacts. In this case it is

almost impossible to know whether it took twenty-five years of exposure or two weeks. The patient states that he has been exposed to jasmine perfume for several years. All he knows is that he gets a bottle labeled jasmine, but he cannot tell whether there has been any change made in the perfume. I think one should try to find out in every case how long it took for the person to become actually sensitized. It may be a short period or a long one. Of course, the condition in this patient is unquestionably due to the perfume mixture.

DR. DAVID BLOOM: The results of the patch tests with the perfume not containing the benzylidene acetone and with the better grade perfume are somewhat baffling, as the areas of contact did not react, while the skin surrounding them gave a positive reaction. It is possible that this reaction was produced by the adhesive tape, to which the patient reacted positively. In my previous patch tests I have eliminated this possible source of error by placing only a small strip of adhesive tape in contact with the skin. The patient will have to be retested with the last two substances in order to clarify this paradoxic reaction.

Scleroderma Due Possibly to Adrenal Neoplasm. Presented by DR. MAURICE J. COSTELLO.

H. N., a woman aged 54, is a Russian Jewess. Her husband and 4 children are living and well. Her mother died of cancer of the stomach, and her brother died of diabetes at the age of 50. Her father, who also had diabetes, died of heart disease. Her paternal grandmother died of diabetes. She has 3 brothers and 3 sisters who are living and well. Ten years ago she had hyperglycemia and arthritis, both of which disappeared after the extraction of a number of teeth. She has lost 20 pounds (9 Kg.) in the past six weeks. The menopause occurred five years ago. She has had pain and soreness of the muscles for the past three months.

The duration of the cutaneous changes is unknown. The eruption is generalized and symmetrically distributed on the neck, back, chest, arms, forearms and lower extremities. It consists of diffuse bandlike areas of shiny, indurated, smooth skin, with an associated brownish pigmentation. The areas of pigmentation for the most part are uniform, but in some patches the pigmented lesions are punctate and discrete. There is limitation of motion of the head, shoulders and knee joints. The patient has difficulty in standing when barefooted because of the severe pains in her legs. The sclerodermatous areas cannot be pinched up, and pressure on the muscles causes pain. There is also stiffness of the fingers. There is enlargement of the left lower part of the thorax external to the ribs, possibly due to thickening of the skin.

Urinalyses consistently showed an acid reaction, a specific gravity of 1.025, a faint trace of albumin, 4.32 Gm. of chlorides (as sodium chloride) and 0.62 Gm. of creatinine per day.

Frequent examinations of the blood showed 13.3 Gm. of hemoglobin per hundred cubic centimeters (78.2 per cent) and 3,920,000 erythrocytes and 8,000 leukocytes per cubic millimeter, with 25 per cent lymphocytes, 4 per cent monocytes, 17 per cent eosinophils, 1 per cent basophils and 53 per cent polymorphonuclear leukocytes. The sedimentation rate was normal. The packed cell volume (average 42 cc.) was 47 cc. per hour. The results of chemical examination of the blood were as follows (per hundred cubic centimeters of blood): nonprotein nitrogen 38.7 mg., urea 18 mg., uric acid 3 mg., chlorides (whole blood) 460 mg., chlorides (serum) 540 mg., sugar (fasting) 63 mg., calcium (serum) 13 mg. and phosphorus (serum) 3.48 mg. The test for phosphatase showed 3 units.

A two dose sugar tolerance test on February 11 showed the following amounts of sugar per hundred cubic centimeters of blood: fasting, 63 mg.; after thirty minutes, 126 mg.; after one hour, 177 mg., and after two hours, 148 mg.

The urine showed a trace of sugar at the end of the two hour period. The fasting and the one hour specimen showed no sugar.

Examination of the stools revealed no ova, parasites or occult blood.

The Wassermann reaction of the blood was negative. A roentgenogram of the chest was normal except that it showed a moderate amount of hilar and peribronchial thickening. A roentgenogram of the abdomen revealed that the kidneys were normal in size and shape. The left one was a trifle lower than normal. There was an oval area, about 1 inch (2.5 cm.) in diameter, located to the right of the spine just above the upper pole of the right kidney. In the lateral view this was seen to be located just anterior to the plane of the vertebrae. It was difficult to identify this lesion definitely, but its location was extremely suggestive of calcifications in the adrenal gland. It was not connected with the biliary tract, but it could have been with a gland. Roentgenographic and fluoroscopic examinations of the gastrointestinal tract showed no abnormalities.

DISCUSSION

DR. DAVID L. SATENSTEIN: The history, the description of the clinical lesions, the condition of the epidermis and the tenderness of the muscles seem to make a fairly classic picture of dermatomyositis. I think that the early part of the history indicates rheumatic infection. I did not see any evidence of scleroderma in this patient.

DR. GEORGE M. LEWIS: I agree with Dr. Satenstein, for the reasons he mentioned.

DR. E. WILLIAM ABRAMOWITZ: I also agree with Dr. Satenstein. While the shadow shown in the adrenal area points to an adrenal condition, it must be considered to be more definitely associated with the cutaneous condition. I think that it is important to exclude a possible parathyroid disturbance in this patient.

DR. HERMAN SHARLIT: I, too, feel this case is one of dermatomyositis. It is probable that the presence of creatinine in the urine substantiates this diagnosis.

DR. LUDWIG OULMANN: I agree with Dr. Abramowitz that the changes in the patient's skin, which I do not regard as evidence of scleroderma, are due to a parathyroid disturbance.

DR. WILBERT SACHS: I cannot make a clinical diagnosis, but I should like to make a suggestion. This patient presents a syndrome similar to Addison's disease. It is known that one of the common causes of this syndrome is tuberculosis of the adrenal glands. Dermatomyositis and Darier-Roussy sarcoid may closely simulate each other. I suggest a biopsy of one of the cutaneous lesions to rule out Darier-Roussy sarcoid.

DR. HERMAN SHARLIT: Dermatomyositis has been described with a minimal amount of cutaneous changes and also with most of the damage in the skin. If the condition in this case is dermatomyositis, the minimal damage is in the skin; but the disease still remains in the same category, even though there is little cutaneous change.

DR. MAURICE J. COSTELLO: A sharply circumscribed shadow at the upper pole of the right kidney was seen on all the roentgenograms. I do not think that it was caused by the barium sulfate given for the gastrointestinal study. Its constant shape, size and location are against it.

This patient also has a low blood pressure for her age, 105 systolic. When I first saw her I thought she had dermatomyositis. She had a thorough work-up before I examined her, and the only significant observation was a high eosinophil count. Her physician thought that she possibly had trichinosis. A case of scleroderma associated with adrenal neoplasm was reported by Barlow (ARCH. DERMAT. & SYPH. **39**:1021-1024 [June] 1939).

A Case for Diagnosis (Cheilitis?). Presented by DR. GEORGE C. ANDREWS.

M. K., a woman aged 35, was first observed two months ago, at which time she complained of dryness, scaling and burning of the lower lip. This condition had been present one year and was growing progressively worse.

Examination shows crusting with erythema and swelling of the entire surface of the vermilion border of the lower lip. The upper lip is normal, as well as the oral mucosa. There are no other cutaneous lesions. A Wassermann reaction of the blood was negative.

A specimen from the center of the lower lip was examined by Dr. Gerald Machacek. He reported that the probable diagnosis was lupus erythematosus, although he could not rule out lichen planus. The penetration of squamous cells into the stroma suggested squamous cell carcinoma.

DISCUSSION

DR. J. FRANK FRASER: Chronic irritation is one of the principal factors in the causation of cancer. A persistent inflammatory lesion of the lip may therefore be regarded as a possible precancerous dermatosis. In regard to Dr. Andrew's case, however, there is no evidence either from the gross appearance of the lesion or in the histologic picture to warrant the diagnosis of epithelioma. There is no epitheliomatous hyperplasia or atypical change in the epithelial cells. In my opinion the case should be recorded as one of chronic cheilitis.

DR. PAUL E. BECHET: I do not think any evidence exists of precancerosis or of cancer. I have seen similar eruptions occur on the lower lip from the use of tooth pastes, without affecting the buccal mucosa, and that possibility should be kept in mind.

DR. ANDREW J. GILMOUR: This woman was using one brand of tooth powder for a long time. My impression is that this condition is cheilitis due to the use of tooth powder. I saw no evidence clinically of epithelioma.

DR. HERMAN SHARLIT: I am inclined to feel that this condition is nothing more than simple cheilitis. Strangely enough, cheilitis is always persistent. It is one of the most difficult things to clear up. I have been treating a patient for three and one-half years, but the cheilitis still persists.

DR. ISADORE ROSEN: I agree with the speakers who believe that this condition is an inflammatory process due to some persistent irritation, such as that caused by tooth paste, mouth washes or similar substances. Inflammatory exfoliating conditions of the lips are frequently seen which last for a long time because the cause is not recognized, but as soon as the exciting factor is removed the process rapidly disappears.

DR. WILBERT SACHS: All that cheilitis means is an inflammation of the lip. Any inflammatory process, therefore, would give this clinical picture. Microscopic examination, however, might reveal the type of inflammation. The epidermis is neither thickened nor acanthotic, but the cells show sufficient change that they can be called anaplastic. Such a process is malignant. There is no tumor of the epithelium and therefore no neoplasm and no epithelioma. In other words, what this slide shows is an anaplastic, nonthickened epidermis beneath which is an inflammatory protective zone. While there is no epithelioma present now, if the condition is permitted to continue for any length of time it is probable that such a neoplasm will develop.

DR. LUDWIG OULMANN: I cannot see any evidence of malignancy clinically or histologically so far. I agree with the diagnosis of cheilitis.

DR. DAVID L. SATENSTEIN: Some one suggested doing nothing but applying a bland ointment for a while but did not say for how long. Should such treatment be kept up indefinitely? Should a bland ointment be used until a neoplasm develops? The condition in this case resembles widespread keratosis. This condition is seen often, and not infrequently early malignant changes are observed before the development of a neoplasm. A bland ointment may be applied for a reasonable length of time, but if there is no improvement, one must accept the pathologist's opinion that the process is malignant and treat it accordingly.

DR. GEORGE C. ANDREWS: I think it would be easy to excise the mucous membrane of the lower lip, undercut the mucous membrane on the inside of the

lip, bring it forward and suture it to the anterior margin. I have done that on occasions with good results.

This condition has been present for about four months. She has been using bland ointments right along. I did not have her stop using the tooth powder because I thought it was bland and harmless. The inner edge of the lip was raised and infiltrated when palpated. It felt hard, and for that reason I did not think the condition was due to a contact irritant, but I may be wrong. I shall tell her to stop using the tooth powder and see whether that makes any difference.

Xanthelasma Associated with Leprosy. Presented by DR. MAURICE J. COSTELLO.

M. M., an American man aged 43, a patient of Dr. Howard Fox, was first seen on March 1, 1935. He stated that he was married, had no children and had been in business in Brazil for twenty years, living in Rio de Janeiro, Brazil. He first noticed a disturbance of sensation in the legs about fifteen years ago (1925). This was followed by severe pain in the ankles. In 1933 an eruption appeared.

When first seen the patient presented a generalized eruption of macules, which was fairly symmetric and profuse on the forehead, trunk and extremities, especially on the left side of the forehead and trunk. The macules were reddish yellow, ill defined, from 1 to 3 cm. in diameter and round or oval; all except those on the forehead showed comparatively little infiltration. The lesions showed appreciable anesthesia to a pinprick. There were thinning of the outer third of the eyebrows and thickening of the ear lobules. There were decided thickening and dulling of sensation of the right ulnar nerve and definite anesthesia of the legs from the knees to ankles, where there were numerous scars, resulting from former traumatism and failure to heal as in a normal person. Nasal smears showed lepra bacilli.

On the lower eyelids there are two poorly circumscribed, irregularly shaped lemon-colored areas differing from xanthelasma in that the lesions are less circumscribed, are lighter in color and have no appreciable infiltration.

Treatment from March 8 to November 6 consisted of the administration of chaulmoogra oil in doses of 1 cc. to 2.5 cc. This gave relief in the beginning. The pain was less and became concentrated in the ankles. He suffered from an attack of leprous fever from November 11 to November 23. The temperature ranged from 101 to 104 F. and was accompanied by an outbreak of numerous red, painful nodules on the body and extremities. From Oct. 5, 1936, to June 22, 1937, the patient suffered less and was occasionally given ethyl chaulmoograte. Administration of this drug was continued from September 15 to October 5. From then until Feb. 9, 1938, the patient was treated with weekly injections of gold sodium thiosulfate not exceeding 50 mg., with no improvement. From March 2, 1938, to March 4, 1939, the patient received ethyl chaulmoograte in doses of 1 cc. to 2.5 cc.

Beginning on March 23, 1939, the patient was given daily injections of thiamine hydrochloride, 20 mg. to each cubic centimeter, and six 3 mg. tablets of thiamine hydrochloride daily. This treatment was continued until April 22, when azosulfamide (disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonate) was prescribed. Sulfanilamide and azosulfamide, three 5 grain (0.3 Gm.) tablets daily, improved the patient's condition, but administration of these drugs was discontinued June 10 because of a toxic reaction. Injections of thiamine hydrochloride were continued until Jan. 16, 1940.

On January 30 the patient was given weekly injections of 1 cc. of cobra snake venom. It was given on February 2, 13, 20 and 27, with slight relief of the severe pain of leprous neuritis.

Since February 22 the patient has had a nickle-sized ulceration of the right elbow region and a linear crusted ulceration on the inner aspect of the left foot and ankle. Capsules containing codeine, acetylsalicylic acid and acetophenetidin afford relief from the pain.

DISCUSSION

DR. LUDWIG OULMANN: I had a case of leprosy of the nodular type under observation for over twenty years. The patient also had xanthelasma.

DR. WILBERT SACHS: It would be interesting to see whether this reaction is a xanthelasma or a sarcoid. In leprosy there is a sarcoid type of reaction, and should such a reaction develop in an area where the skin is thin, as it is on the eyelids, it may give a yellow color to the lesion and simulate xanthelasma.

DR. DAVID BLOOM: It would be of interest to know if these xanthelasma-like lesions show the usual changes of xanthelasma or not and if these lesions are directly due to the effect of the lepra bacilli.

DR. DAVID L. SATENSTEIN: I have seen lesions like this on the eyelids and also on the conjunctiva in patients with the late stages of leprosy.

DR. MAURICE J. COSTELLO: Hopkins, Black and Rose (ARCH. DERMAT. & SYPH. **39**:239-252 [Feb.] 1939) in their survey of 243 lepers in the national leprasorium stated that xanthelasma associated with leprosy was found in 27 (11 per cent) of the cases. The lipoid contents of the blood showed decided variation, especially in the cholesterol esters. Postmortem examination of 96 lepers showed disease of the liver in almost all cases. Xanthelasma was not seen in any of 235 tuberculous patients. A similar examination of 200 patients in the outpatient department of a large clinic disclosed 2 with xanthelasma. This man does not present xanthelasma lesions as they usually are. They are diffuse, lemon yellow and not sharply circumscribed.

Dermatitis Artefacta. Presented by DR. PAUL E. BECHET.

E. G., a woman aged 36, came to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, stating that a lesion had been present for six years and had followed a hot water burn. She was positive that it had never shown any tendency to heal in that long interval. On the outer aspect of the lower part of her right leg a group of crusted lesions, about 5 by 10 mm. in diameter, may be observed, which appear to be extremely superficial and acute, despite the history of six years' duration. There is no infiltration or atrophy.

DISCUSSION

DR. MAX SCHEER: I suggest putting the patient in a plaster cast from the ankle to the hip.

DR. PAUL E. BECHET: The evidence in favor of the diagnosis of an artefact is convincing. The acute, superficial, inflammatory, excoriated appearance of the lesions is against the history given of six years' duration.

Livedo Racemosa Type of Tertiary Syphilis. Presented by DR. MAURICE J. COSTELLO.

E. J., a housewife aged 32, was previously presented before this society in February 1940 (ARCH. DERMAT. & SYPH. **42**:392 [Aug.] 1940). During the past two weeks a similar eruption has been developing on the lower third of the inner aspect of the right thigh and on the inner aspect of the right leg. The Wassermann reaction of the blood remains negative.

DISCUSSION

DR. PAUL E. BECHET: There is a definite history of direct and frequent contact with a hot radiator. The eruption presents the typical reticulated appearance of an ordinary erythema ab igne. On the other hand, there are nodules and considerable infiltration. The most plausible explanation, it seems to me, would be to consider that the patient had a primary erythema ab igne and that, owing to a locus minoris resistentiae, a syphiloderm developed on it.

DR. GEORGE M. LEWIS: This case is interesting. The infiltration of the lesions suggests something more than erythema ab igne. I think the presenter is correct in his conception.

DR. WILBERT SACHS: I think the process is progressing. New lesions are developing. I have many sections from patients with tertiary syphilis which do not show necrosis.

DR. DAVID L. SATENSTEIN: As Dr. Bechet said, when a syphilitic patient gets a trauma of any kind, a syphilid develops. There is no pigment in this particular tissue. There are telangiectasis, irritation of the wall of the vessel and a good deal of inflammatory reaction, and among the cells some plasma and giant cells can be found, which are sufficient evidence to take the condition out of the group of erythema ab igne and put it in some other group. Because of the history in this case, I suggest that the condition possibly might be a syphiloderm. After seeing the patient tonight, I am convinced that the lesions are syphilitic, because a similar process has developed on the other leg.

DR. ISADORE ROSEN: I was interested in seeing this patient for a second time. I still believe that the entire process is one due to vascular injury sustained by the excessive heat directly applied to these areas. If the condition were syphilitic, involvement of such superficial blood vessels would be followed by ulceration. The infiltration that this patient presents is due to the reaction produced by long-continued contact with heat.

DR. MAX SCHEER: In erythema ab igne no infiltration can be felt. If one runs a finger over these lesions, one can feel definite infiltration, which I think speaks strongly in favor of a diagnosis of livedo reticulata syphilitica.

DR. GEORGE C. ANDREWS: I have the impression that some of that thickening is keloidal. The woman has had syphilis, but I hesitate to accept the fact that syphilis produced these lesions.

DR. E. WILLIAM ABRAMOWITZ: In my opinion, there is still the possibility that this condition is erythema ab igne. I have seen erythema ab igne in which crusts developed. I am not convinced that this particular patient has a syphilitic lesion.

DR. WILBERT SACHS: Because the lesion is superficial it gives the clinical picture of erythema ab igne. If the process were deep, the clinical picture would be different. All syphilitic lesions do not go on to necrosis.

DR. MAURICE J. COSTELLO: The first dermatologist who saw this patient said she had syphilis and gave her injections of a bismuth compound. The following week I saw her and said the condition was erythema ab igne. The Wassermann reaction of the blood has been negative on several occasions. Everybody agreed except Dr. Satenstein, who said the condition was livedo racemosa type of tertiary syphilid (Ehrmann, in Transactions of the Sixth International Dermatological Congress, New York, 1908, vol. 2, p. 763). This woman sat on a radiator for a certain number of hours every day while sewing, and she was unaware of the eruption until her husband noticed it. She does not know how long it has been there. The parts of the other leg that are involved are those that were partially in contact with the radiator.

Amyloidosis Cutis (Localized). Presented by DR. E. WILLIAM ABRAMOWITZ.

I. R., a man aged 54, came to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital in July 1939, with an eruption on the legs, buttocks and abdomen of two years' duration.

There are grouped papular lesions on the flanks and buttocks. These have been present for the past three years. The extensor surfaces of both legs are almost completely covered by discrete, pinhead-sized yellowish brown infiltrated papules and areas of lichenification.

The Wassermann and Kahn tests gave negative reactions. The histologic report was amyloidosis. The complete blood count was normal, and the sugar content of the blood was 55 mg. per hundred cubic centimeters. The congo red test gave a positive result.

DISCUSSION

DR. MAX SCHEER: I suppose I shall have to accept the diagnosis since it was confirmed histologically, but clinically the condition looks like neurodermatitis.

DR. J. FRANK FRASER: I agree with Dr. Abramowitz' diagnosis.

DR. PAUL E. BECHET: I do not agree with the diagnosis. This man has a tremendous amount of pruritus. In my opinion the eruption resembles neurodermatitis rather than amyloidosis.

DR. DAVID L. SATENSTEIN: Eruptions of amyloidosis are itchy, and the patients scratch and get secondary changes in the skin which cover the primary changes. The primary changes are found only on microscopic examination. This case is a proved one of amyloidosis.

GEORGE C. ANDREWS, M.D., *President*

ANTHONY C. CIPOLLARO, M.D., *Secretary*

April 9, 1940

Urticaria Pigmentosa (Bullous Type). Presented by DR. WILBERT SACHS.

B. M., a white baby aged 6 months, was first seen by me on March 26, 1940. There are three angiomatous lesions, which have been steadily increasing in size since birth. The child also has a generalized eruption, which appeared one hour after birth. The eruption first was noticed on the extremities, and in a few weeks it has spread to the face, scalp and body.

The dermatitis is composed of irregular, somewhat oval lesions which vary in diameter from 1 to 5 cm. Some of the lesions are flat, and others are slightly raised. They vary in color from a light tan to a deep brown. Some have become bullous without any apparent trauma. With the slightest trauma large bullae are easily elicited on any of the lesions.

All laboratory examinations of both the parents and the child gave negative results.

DISCUSSION

DR. HERMAN SHARLIT: It is my understanding that urticaria pigmentosa is an inflammatory disease. Therefore, the congenital appearance of the eruption would be unusual. I am not at all certain that this child was born with this disease, but if that is the case, I should be inclined to consider the condition in the category of a nevus.

DR. DAVID L. SATENSTEIN: This case is the most atypical one I have ever encountered. I should never have made that diagnosis. I do not even recall reading of urticaria pigmentosa associated with bullous formation. I never saw such large lesions before. Congenital conditions may not be manifested until the first few hours of life. Various nevi manifest themselves a few hours after birth. Lesions of this disease may be nodular. I have some interesting specimens of nodular lesions. The difference between congenital and acquired conditions is that in the congenital type there is no inflammatory reaction but in the acquired type there is considerable inflammatory reaction, in which are mass cells.

DR. HOWARD FOX: There are two unusual features in this case. One is the appearance of the eruption practically at birth, and the other is the presence of bullae. Contrary to the statement of one of the members, I do not think the large size of the lesions is unusual. In fact, this size is rather typical of the conditions which occur in infants and in children. I have numerous photographs of rather large lesions in children. One of the clinical differences between the type seen in children and the acquired type of adults is the size of the lesions. In the former they are the size of small coins, whereas in the latter they are apt to be the size of a split pea or smaller.

DR. WILBERT SACHS: I should not have shown a patient with ordinary urticaria pigmentosa. I showed this patient because of some of the unusual features that are present.

A Case for Diagnosis (Keloid? Kaposi's Sarcoma?). Presented by DR. E. WILLIAM ABRAMOWITZ.

F. M., a woman aged 49, came to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital in March 1940 with an eruption on the dorsum of the left hand of two years' duration.

The patient presents on the dorsum of the left hand several firm, erythematous, elevated, nodular lesions, about the size of a dime. There is no history of trauma.

The histologic report states: "There is organizing granulation tissue, suggesting an early keloid" (Dr. Satenstein). The results of Wassermann and Kahn tests were negative.

DISCUSSION

DR. MAX SCHEER: I think the lesion is a keloid.

DR. MIHRAN B. PAROUNAGIAN: I suggest the possibility of sarcoma rather than keloid. The dark brownish color is unlike a keloid.

DR. ANDREW J. GILMOUR: I think granuloma annulare has to be excluded.

DR. GEORGE M. LEWIS: It is my impression that the condition is a hypertrophic scar rather than a keloid.

DR. ISADORE ROSEN: I saw this patient when she was first admitted to the hospital, and the clinical features are different tonight. At the time of admission the lesions were raised, fairly firm and globular. There was a definite violaceous color, best described as the color seen in Kaposi's sarcoma, and there was no reaction around the lesion itself. My impression was that of either granuloma annulare or sarcoid, although I kept in mind the possibility of Kaposi's sarcoma. There is a change in all of the clinical features now. The lesions have become flatter; the color has faded, and the lesions seem to be in the process of involution. Now I should be more inclined to make a diagnosis of granuloma annulare.

DR. DAVID L. SATENSTEIN: I do not know why Dr. Rosen is astounded because of the change of color; the vasodilatation has probably subsided. There was fibrous tissue growing in all directions, with a few blood vessels in the cutis. The blood vessels were somewhat dilated. There was no elastic tissue in the lesion, which is one of the features of a hypertrophic scar. I did not make a diagnosis of keloid; in fact, I made no diagnosis. There is nothing suggestive of granuloma annulare, sarcoid or sarcoma.

DR. PAUL E. BECHET: I think another biopsy should be made, as in my opinion the patient does not show clinical signs of a hypertrophic scar or keloid. There is infiltration but not the hard infiltration usually found in a keloid or in a hypertrophic scar. I am inclined to place the lesion in the tuberculoid group and suggest sarcoid of Boeck as the diagnosis.

DR. E. WILLIAM ABRAMOWITZ: There is no hypertrophic scar or keloid formation. I regard the condition as a sarcoid.

DR. DAVID BLOOM: I saw the patient at the clinic and considered the diagnosis of erythema elevatum diutinum. The lesions looked more violaceous than they do today.

DR. HERMAN SHARLIT: I am inclined to feel that the histologic picture must control one's judgment in this case. The lesions are made up of cicatrizing tissue. Originally this condition might have been a single nodule of Kaposi sarcoma, but this picture is not revealed in the sections now. It is possible for a Kaposi lesion to have undergone cicatrization so that its original character has been obliterated.

DR. DAVID L. SATENSTEIN: I have seen many specimens of Kaposi's sarcoma, but I have never seen a Kaposi lesion become fibromatous. Such a change is

possible, but I have never seen it in any specimens that I have examined. If Dr. Sharlit has any reference to this fact or assumption, I wish he would let me have it.

DR. HOWARD FOX: I think the histologic diagnosis should stand, though I thought the clinical appearance was that of sarcoid. Histologic examination would at least settle the question as to whether the condition is a keloid or the tuberculoid reaction of sarcoid.

DR. DAVID BLOOM: Does the histologic picture exclude absolutely the diagnosis of erythema elevatum diutinum? In the case presented a few years ago as one of erythema elevatum diutinum (ARCH. DERMAT. & SYPH. **39**:369 [Feb.] 1939), there was considerable fibrosis present in some of the lesions.

DR. DAVID L. SATENSTEIN: As far as I know, this picture excludes the diagnosis of erythema elevatum diutinum.

DR. E. WILLIAM ABRAMOWITZ: In view of the histologic picture, I believe one can rule out a diagnosis of hypertrophic scar or sarcoid. The disappearance of one lesion after a biopsy specimen was taken is not in favor of a keloid. It is possible that another biopsy may show granuloma annulare.

Telangiectatic Nevus. Presented by DR. DAVID BLOOM.

B. F., a woman aged 22, came to seek advice about an eruption on the right side of the face which had been present as long as she could remember.

The eruption consists of numerous telangiectatic lesions, some of which suggest spider nevi. It extends from 1 inch (2.5 cm.) above the right eyebrow downward, involving the upper eyelid, the right side of the nose, the upper lip and the vermilion border of the lip, the temple and the cheek. It involves also the right eye, for the carunculus and the conjunctiva of the bulbus also present telangiectasias. The region of the eye has been involved for the past three years only, the condition gradually becoming more conspicuous. There are also several telangiectatic lesions on the left side of the face and on the right shoulder.

The patient states the belief that in the last few years there has been an increase in the number of the lesions.

No history of bleeding has been obtained. The family history shows no abnormalities of this kind.

DISCUSSION

DR. DAVID L. SATENSTEIN: Electrolysis is the only therapy and is to be used with caution to avoid minute pits.

DR. DAVID BLOOM: This case is presented because of the rarity of this type of nevus. As these dilated blood vessels are situated superficially, I believe it is possible to destroy them by electrolysis without any resultant scars.

Multiple Angioma. Presented by DR. MIHRAN E. PAROUNAGIAN.

J. K., a boy aged 11 months, was brought to me for the removal of the lesions. The total number of lesions is nine, and they are distributed as follows: one on the left side of the neck, one on each arm, two on the left side of the trunk, one on the right side of the trunk, one on the shoulder and one on a digit. They vary in size from that of a pea to that of a hazelnut. They are deep red; most of them are elevated, and some have the appearance of a raspberry. They have existed since birth, and the mother stated the belief that they are getting larger. The patient is presented for therapeutic suggestions.

DISCUSSION

DR. FRED WISE: I should use radium on the small lesions and excise the large lesions.

DR. GEORGE C. ANDREWS: I feel that the simplest way to treat this patient is excision for most of the lesions and radium treatment for a few of them. They

could be treated with injections, with solid carbon dioxide and in other ways, but the procedure would be long drawn out. If they are excised, the patient will be all right in a week or two.

DR. E. WILLIAM ABRAMOWITZ: I should like to know what would happen if these lesions were left alone.

DR. HOWARD FOX: The question of spontaneous disappearance of hemangiomas has been discussed at length by members of the New York Dermatological Society. I have long been of the opinion that practically all nevi of this type disappear without treatment before adult life is reached. Traumatism undoubtedly causes a cure in some of the cases.

DR. GEORGE C. ANDREWS: I have seen adult patients with superficial capillary angiomas around the eyes that began as port wine marks which then became nodular, persisted through life and ultimately became large, repugnant lesions.

DR. MIHRAN B. PAROUNAGIAN: I never saw a patient with as many lesions as this one presents. I am grateful for the suggestion as to the therapy.

DR. GEORGE C. ANDREWS: I think it might be a good plan to let the patient alone for about a year and then excise the lesions.

DR. ANDREW J. GILMOUR: Some lesions like these can be improved with continuous pressure. This can be accomplished with a gauze pad and adhesive plaster.

A Case for Diagnosis (Syphilid? Psoriasis?). Presented by DR. ISADORE ROSEN.

M. S., a Negro aged 47, came to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on April 1, 1940, with an eruption on the elbows of seven years' duration and an eruption on the penis of three months' duration.

The eruption consists of small plaques composed of violaceous, erythematous papules.

The Wassermann and Kahn reactions of the blood were negative.

The histologic examination showed the condition to "fit in with secondary syphilis (not lichen planus) but not to be sufficiently advanced for positive diagnosis" (Dr. Satenstein).

DISCUSSION

DR. DAVID L. SATENSTEIN: I found no changes that would suggest any clinical entity, except that the plasma cells might perhaps indicate syphilis. But I have seen plasma cells in some of the "ids" as well as in secondary syphilis.

DR. HOWARD FOX: I think this condition is psoriasis. On three occasions the serologic reaction has been negative. The patient has had some type of eruption for the past ten years, and a few of the lesions have micaceous scales. It is true that psoriasis is rare in full-blooded Negroes, but this patient has an admixture of white blood.

DR. PAUL E. BECHET: I am in favor of the diagnosis of psoriasis. There is nothing clinically that suggests lichen planus. There are no shiny dry papules, and the lesions consist of reddened patches with adherent scales.

DR. DAVID L. SATENSTEIN: I am amused to hear that the condition is psoriasis. Under the microscope there is nothing in the tissue suggestive of psoriasis. I think that the patient has an eczematous reaction in the skin. What the primary condition was I do not know. At present the condition is a secondary process, but it is not psoriasis.

DR. WILBERT SACHS: The lesions on the elbows are psoriatic, but I do not feel that the one on the penis is a psoriatic lesion. The fact that plasma cells are present would be strongly against a diagnosis of psoriasis. Besides, the patient has dermatophytosis of the toes. It is possible that the penile lesion may be an "id."

A Case for Diagnosis (Chronic Ulceration of the Tongue). Presented by Dr. Isadore Rosen.

S. G., a woman aged 23, came to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital in March 1940, with a lesion on the tongue of five years' duration.

The condition began after some dental work was done, and during the five years it healed entirely and remained healed for a number of months. Then it recurred. There is a history of acute exacerbations, with associated pains shooting through the tongue. There are no palpable glands.

The lesion is in the central portion of the right rim of the tongue. It consists of an irregular, superficial, smooth ulceration covered with a grayish exudate. No nodules can be seen. There is no evidence of scar tissue other than the biopsy scar.

Histologic examination revealed a prickle cell epithelioma of the tongue (Dr. Satenstein). The Wassermann and Kahn reactions were negative.

DISCUSSION

Dr. David L. Satenstein: Histologically this condition is as characteristic of an early stage of an infiltrating prickle cell epithelioma as any I have ever seen. It is superficial, but there are strands of cells extending down from the epidermis; there is a malignant dyskeratosis, and in one area the start of whorl and pearl formation can be seen. If this picture does not indicate epithelioma, then I am not acquainted with epithelioma. Five years ago that patient had a traumatic ulcer, which healed. Then it was probably injured again from time to time and now there is a small soft exuberant lesion. It has healed a little since I saw it last week. I do not see anything clinical that would be against the diagnosis of a neoplasm in the early stage of development.

Dr. George M. Lewis: The lesion did not impress me clinically as an epithelioma, and I should hesitate to advise radical surgical removal.

Dr. J. Frank Fraser: Without venturing an opinion regarding the origin of this lesion, I disagree with the diagnosis of epithelioma. The fact that the patient is below the cancer age does not exclude the possibility of malignancy, but when cancer develops in the young it usually runs a rapid course, with a fatal termination. This lesion has been present for five years without apparent evidence of malignancy, such as regional infiltration or metastasis to the lymph nodes. The average duration of life in cases of untreated cancer of the tongue is from eighteen months to two years.

In regard to the microscopic picture in the section presented, I found none of the histologic signs of malignancy. My attention has been called to the presence of dyskeratosis and the so-called epitheliomatous hyperplasia. These features are not pathognomonic of a malignant growth. They are found frequently in inflammatory diseases and in granulomas (such as blastomycosis and tuberculosis).

Dr. Anthony C. Cipollaro: I hesitate to enter into a discussion after having listened to Dr. Satenstein and Dr. Fraser, but disregarding their discussion and purely on clinical grounds, I should make an unequivocal diagnosis of prickle cell epithelioma in this case. I should disregard the history the patient gave—that the condition has been present for five years—and should treat the lesion as a squamous cell epithelioma of the tongue.

Dr. Howard Fox: The difference of opinion expressed by two excellent histologists encourages me in my opinion that this condition is a papilloma and not an epithelioma. Either the present lesion or some other type of lesion has been present on the tongue for five years, an unusual length of time for a squamous cell epithelioma. Furthermore, epithelioma of the tongue is rare in women and especially so in young women.

Dr. David L. Satenstein: Those who study cancer tissue know that when the lesion is marginated by an intact basal cell layer, one does not find any nodes. This lesion is still within the epidermal margins; so there are no nodes. At present the lesion is still amenable to local therapy.

DR. WILBERT SACHS: If this patient were twenty or thirty years older and presented this clinical and microscopic picture, the diagnosis of early prickle cell epithelioma would readily be accepted.

DR. FRED WISE: I agree with Dr. Cipollaro with respect to excision, disregarding the history. I believe the lesion should be treated radically, because I suspect it is malignant.

DR. HERMAN SHARLIT: Cases of this kind offer the most trying problem to the dermatologist. If the condition were unquestionably an epithelioma of the tongue, what would be the type of therapy? There are suggestions of radical therapy and of conservative expectant therapy. The decision is a serious one. Fundamentally the difficulty lies in the fact that from the histologic picture one cannot be certain as to what will be the clinical eventuation as a result of expectant treatment.

DR. DAVID L. SATENSTEIN: When a lesion is marginated by a basal cell layer, the process is local, and local therapy is sufficient; but when the lesion breaks through and disseminates, radical therapy is necessary. Epitheliomas do not start in normal tissue. There must be a preceding process. In any type of epithelioma, even a basal cell neoplasm, there are changes taking place in the skin before the epithelioma develops.

DR. ISADORE ROSEN: I still am in doubt as to the interpretation of the microscopic picture. I intend showing the slide to two or three other pathologists for their opinion. It happens often that pathologists disagree regarding the interpretation of cellular changes in cases of this type. On account of the insistence of the patient regarding the course during the past five years (healing and recurrence), I shall delay radical procedure.

Lupus Erythematosus of the Mucous Membranes. Presented by DR. DAVID BLOOM.

M. P., a woman aged 25, came to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on March 29, 1940, with an eruption on the face of one year's duration.

On the left ala nasi there is a round, nickel-sized, ill defined, erythematous lesion, which is crusted and atrophied in the center. On the cheeks and on the chin there are a number of lentil-sized to pea-sized, round or irregularly shaped, erythematous, scaly, atrophic lesions. The conchae of the ears are similarly involved. The lower right eyelid is devoid of eyelashes, and along the margin there are several erythematous, scaly, atrophic lesions. The edge of the eyelid itself is erythematous and telangiectatic. This erythema extends also into the conjunctiva of the lid. The edge of the left lower eyelid and the conjunctiva of this lid are similarly but less involved. Here the conjunctiva palpebrae presents well defined, erythematous lesions. The mucous membrane of the right cheek shows a nickel-sized round lesion with milky reticulation and telangiectasia.

The Wassermann and Kahn reactions were negative. A complete blood count was normal except for a slightly higher percentage of young polymorphonuclear leukocytes. The histologic examination of one of the lesions on the cheek showed "early lupus erythematosus" (Dr. Satenstein).

A Case for Diagnosis (Syphilis? Psoriasis?). Presented by DR. ISADORE ROSEN.

L. M., a Negress aged 28, came to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on April 5, 1940, with an eruption on the face, body and extremities of four weeks' duration. The lesions, especially on the extensor surfaces, are guttate to coin sized and larger. Some show heaped up micaceous scales, while others are moist and covered with lamellated crusts, giving the appearance of rupioid lesions.

Dark field examination of smears of material from the moist lesions gave negative results. The Wassermann and Kahn reactions were negative.

Histologic sections were reported to "fit in with psoriasis" (Dr. Satenstein).

DISCUSSION

DR. DAVID BLOOM: In spite of the serologic and histologic reports, I cannot make a definite diagnosis of psoriasis, for there are many lesions which are fleshy in appearance and not covered entirely with scales. These features demand repeated serologic tests and a therapeutic test with arsphenamine.

DR. DAVID L. SATENSTEIN: There is nothing special to report. The biopsy specimen was from one of the lesions that Dr. Rosen thought might be syphilitic. The appearance was typical of psoriasis.

DR. MAX SCHEER: I have seen patients with a psoriasiform syphiloderm whose Wassermann reactions were negative for months and became positive later.

DR. ISADORE ROSEN: I believe that the diagnosis of psoriasis cannot be accepted without reservation. From a clinical standpoint, I admit that some of the lesions are strongly suggestive of psoriasis; on the other hand, there are lesions that are moist, conical in shape and covered with a rupioid or lamellated crust which certainly is not a characteristic of psoriasis. Although the Wassermann reaction was negative, I have presented before this society a number of patients with active manifestations of syphilis in whom the Wassermann reaction was negative.

Erythroplasia of Queyrat. Presented by DR. ISADORE ROSEN.

B. C., a man aged 24, came to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on March 4, 1940, with an eruption on the glans penis of three years' duration.

On the glans penis, extending to beyond the sulcus, is a brownish red lesion the size of a 25 cent piece, irregular in outline, somewhat edematous and covered with a crust. There are no lesions elsewhere on the body.

Histologic examination showed the condition to be erythroplasia of Queyrat (Dr. Satenstein). The Wassermann and Kahn reactions were negative.

DISCUSSION

DR. WILBERT SACHS: I think this case is the eighteenth or nineteenth one of erythroplasia that has been reported in the American literature. Of course, I realize that many more cases must have been encountered, but they have not appeared in the literature. I failed to find a single report in the American literature in which it was stated that the lesion became malignant. For the time being I do not think any heroic treatment should be instituted, because in seven years not a single lesion became malignant.

DR. HOWARD FOX: I have shared the opinion of Dr. Sachs for some time that dermatologists are unnecessarily concerned about the danger of malignant changes in this disease. In many cases the penis has been badly mutilated by destructive methods of treatment. I have a patient 75 years old who has had red, beefy, slightly oozing areas on the glans penis for the past twenty-five years. They have never been treated.

DR. WILBERT SACHS: Dr. Satenstein showed a patient for me two or three years ago who had eight lesions somewhere on the glabrous skin. One of the lesions was on the nose. These lesions entirely cleared up under mild therapy, but recently some reappeared. Three biopsy specimens were taken, one from the glans penis and two from the skin. The histologic picture of each specimen showed erythroplasia, the same pathologic features as shown by this patient.

DR. DAVID BLOOM: When I saw the patient the first time at the clinic the lesion was crusted and looked more like psoriasis than erythroplasia. Today the lesion presents a velvety, clean appearance considered typical for erythroplasia. I am wondering if he has been applying any ointments which might have changed the appearance.

DR. FRED WISE: In my personal experience, the best results have been obtained from electrodesiccation.

DR. DAVID L. SATENSTEIN: According to the French literature, some lesions like this recur and some become malignant.

DR. GEORGE C. ANDREWS: I had a case in which the disease was diagnosed as erythroplasia histologically by Dr. Machacek. Clinically I thought the condition was erythroplasia. Another biopsy specimen was taken from another part of the lesion, and the diagnosis was squamous cell epithelioma. The man died. I had another case in which the diagnosis erythroplasia was made by an eminent dermatologist and by me. The patient went to Europe, and the condition was diagnosed suppurative balanitis. He was given 5 per cent yellow mercuric oxide ointment, which was used for months, with complete cure.

DR. MAX SCHEER: There is a report in the French *Bulletin* of a case in which a patient had enlarged inguinal nodes which on microscopic examination were found to be invaded by squamous cell cancer; later on erythroplasia of the penis developed.

DR. ISADORE ROSEN: I believe that many so-called cases of erythroplasia were really cases of psoriasis, the lesions occurring only on the glans penis. It is possible that in some patients malignant conditions develop as the result of excessive treatment with roentgen rays.

BRONX DERMATOLOGICAL SOCIETY

MARION B. SULZBERGER, M.D., *President*

HENRY SILVER, M.D., *Secretary*

March 28, 1940

Herpes Gestationis. Presented by DR. MAX B. KAMPF.

F. W., a housewife aged 34, was first seen at the clinic of the Fordham Hospital on Jan. 16, 1940. She was then in her fifth month of gestation. There had been four previous pregnancies, of which two terminated at full term, one was a miscarriage and one terminated in a curettage after an incomplete abortion.

The cutaneous eruption appeared about ten days prior to the patient's first visit to the clinic. It consisted of erythema, grouped vesicles, many large bullae and a number of crusted lesions. The lesions were first seen on the upper and lower extremities and then spread to the trunk. The patient complained of intense itching.

Examination of the blood showed 90 per cent hemoglobin and 4,620,000 red cells per cubic millimeter, with 35 per cent polymorphonuclear leukocytes, 28 per cent staff forms, 25 per cent lymphocytes, 9 per cent eosinophils and 3 per cent monocytes. The Wassermann and Kahn reactions were negative.

The patient received injections of a preparation of corpus luteum (proluton) twice weekly from February 1 until February 20. This medication seemed to lessen the itching, and the lesions on the abdomen and thighs showed a tendency to clear.

DISCUSSION

DR. ADOLPH ROSTENBERG: This case is of particular interest to me as I have recently studied similar ones. The most striking case under my observation was that of a woman in whom the condition developed soon after delivery. She presented bullae of enormous size and was seriously ill for several months.

Herpes gestationis was first described by Milton under this name in 1872, but the condition is now considered a form of Duhring's disease. There is no doubt of the endocrine influence in the causation of these conditions. It is therefore

possible that the lutein which Dr. Kampf is using is responsible for the improvement. In my case the excretion of gonadotropin in the urine was protracted for several months after the confinement.

DR. FRANK E. CROSS: There is no question as to the diagnosis. These cases are not common. Yet I have encountered 5 or 6. One patient had the disease during three of her four pregnancies. In another patient the eruption appeared soon after the child was born.

DR. ARTHUR SAYER: I have been especially interested in this disease because of the intimate experience that I had in my family on two separate occasions. Herpes gestationis, in my opinion, is due to a toxic disturbance induced by impaired hepatic function. This was demonstrated by tests for hepatic function, which showed moderate impairment. Apparently the liver is unable to cope with the added burden of fetal metabolism and fails to function in its usual role of detoxication. This results in the bullous eruption associated with severe pruritus.

In the case which occurred in my family fifteen and eighteen years ago, a variety of treatments, such as the administration of calcium and sedatives and the transfusion of blood from normal pregnant women, was tried, without benefit. However, following delivery there was dramatic improvement in the patient's condition; the itching subsided within a few hours and the eruption rapidly disappeared.

Another point to be emphasized is that the disease usually occurs during the first pregnancy and repeats itself in subsequent pregnancies.

DR. DAVID BLOOM: It has been observed that patients suffering from herpes gestationis frequently have a history of stillbirth or of the child's dying soon after birth. The history of stillbirth and miscarriage in this case may, therefore, be a part of the disease.

DR. MAX B. KAMPF: Since the administration of proluton no vesicles or bullae have appeared. It seems that this therapy was of decided benefit in this case.

Early Syphilitic Macular Atrophy. Presented by DR. HENRY SILVER.

V. A., a window cleaner aged 36, born in Finland, came to the clinic of Mount Sinai Hospital on Aug. 15, 1939. Examination revealed a hunterian chancre on the penis and an extensive eruption consisting of large papular lesions involving the face, neck, arms, buttocks, upper part of the back and abdomen. There were few lesions on the chest. A mucous patch was seen on the right tonsil. Examination showed the presence of spirochetes. The Wassermann reaction was 4 plus.

Treatment with eight injections of trisodarsen (the trisodium salt of 3,3'-diamino-4,4'-dihydroxyarsenobenzene-N,N'-dimethylene sulfonic acid) and twenty injections of bismuth subsalicylate caused rapid involution of the lesions. In November 1939 and January 1940 the Wassermann reaction was negative.

The patient was seen at frequent intervals, and the process of transformation of the syphilitic papule into a macular atrophic lesion was observed. First the papules became flat, and the color changed to livid red, with surrounding peripheral pigmentation. The lesions soon reached the level of the skin. On palpation the skin was found to be thinner than normal. The color then changed to violet, and the surrounding pigmentation became less evident as the wrinkling and atrophy became more manifest.

At present there are on the back extending down to the sacrum and on the sides of the chest and the lower part of the abdomen many bluish red or whitish lesions varying in size from that of a lentil to that of a large pea. The lesions are soft and baggy, and their surface is wrinkled The phenomenon of herniation, while present in a few lesions, is not pronounced.

Histologic examination of tissue from a lesion on the upper part of the back showed the epidermis to consist of five to seven layers of cells. Most of the papillary bodies were flattened. Aside from this beginning atrophy, the epidermis showed no other pathologic changes. The papillary and subpapillary layers showed

rather dense infiltrates of lymphocytes around the blood vessels. There was also inflammatory exudation around the hair follicles consisting mainly of fibroblasts and leukocytes. The elastic tissue was greatly reduced in amount. The histologic diagnosis was early macular atrophy.

DISCUSSION

DR. CHARLES WOLF: The lesions are steadily improving. The eruption is probably caused by the rapid absorption of the inflammatory exudate as the result of therapy. The eruption was of the precocious type; the lesions were large and were seen several months after the appearance of the initial lesion. In my opinion this condition is not macular atrophy but pseudoatrophy and these lesions will disappear in time.

DR. DAVID BLOOM: I do not think that definite atrophy of the skin can disappear. In this case the atrophy is of the ballooning type, which will never disappear.

DR. THEODORE ROSENTHAL: I have seen secondary syphilis terminate in a similar eruption, and I agree with Dr. Silver's diagnosis.

DR. LOUIS CHARGIN: There are two types of macular atrophy, primary and secondary. Primary macular atrophy is a disease sui generis, while secondary atrophy follows in the wake of a preceding disease. Primary atrophy has a characteristic picture. It appears in the form either of anetoderma Jadassohn or of anetoderma Schweninger-Buzzi. The end in both types is alike, showing the characteristics of herniation, and at this stage the origin cannot be identified. Secondary atrophy follows in the wake of such diseases as syphilis, tuberculosis, leprosy and lichen planus. I have never observed such an early stage of the disease as in the case presented. There is no doubt that the condition is macular atrophy following a large papular syphiloderm, and this diagnosis is confirmed histologically by the characteristic loss of elastic tissue.

DR. PAUL GROSS: Although the end results of primary and secondary atrophy may be the same, one can sense the fundamental difference which is suggested by the facts that the inflammatory reaction of primary macular atrophy is slight and that the result of atrophy is out of proportion to the preceding clinical aspect. In the case presented the preceding eruption was a large papular syphilid and the inflammatory process was intensive. This could account for the decided secondary atrophy.

DR. SAMUEL M. PECK: In my opinion there is damage to the elastic tissue in all inflammatory processes. If complete degeneration takes place, atrophy results. It might be worth while to consider the possibility that just as some persons react to an inflammatory process with a keloid, others might react with atrophy. On the one hand there is a tendency to overproduction on the part of the collagen, and on the other hand the elastic tissue is unusually sensitive to toxic processes, so that no regeneration of the elastic tissue takes place and atrophy results. Such a conception would explain the macular atrophy in the case under discussion.

DR. HENRY SILVER: Syphilitic macular atrophy is frequently observed. What makes the case of unusual interest is the actual observation of the transition of syphilitic papular lesions into macular atrophic lesions and the histologic observation of early disappearance of the elastic tissue. Only a few authors have been fortunate to see and record the actual transformation. Reports of this type have been given by Pellagatti and others (Silver, H., and Chargin, L.: Syphilis and Macular Atrophy, *Urol. & Cutan. Rev.* **37**:395-402, 1933. Chargin, L., and Silver, H.: Macular Atrophy of the Skin, ARCH. DERMAT. & SYPH. **24**:614-643 [Oct.] 1931).

The eruption presents three stages of transformation: (1) the involution of the papule, (2) changes in color of the lesions and (3) wrinkling and atrophy. The transformation in my case was fairly rapid, taking place in less than two months. A large number of the lesions are still in the process of transformation. It is expected that in a few months the patient will present the fully developed picture of macular atrophy.

Pigmentation Following Lichen Planus. Presented by DR. CHARLES PINES.

G. P., a Negro waiter aged 30, is under treatment at the central social hygiene clinic of the department of health for late latent syphilis. In November 1939 there developed a moderately pruritic cutaneous eruption, which consisted of small angular or polygonal flat violaceous papules with glistening tops, which was readily recognized as lichen planus. The eruption was limited to the chest, the back and the flexor surfaces of the arms. The histologic examination corroborated the clinical diagnosis of lichen planus.

Prior treatment consisted of injections of arsphenamine and of a bismuth compound. After the appearance of the lichen planus antisyphilitic treatment was continued. In about eight weeks the lesions had undergone involution, leaving a brownish black pigmentary residue. It was interesting, however, to note that the generalized pigmentation was not limited to the previous sites of the lesions of lichen planus.

DISCUSSION

DR. ADOLPH ROSTENBERG: In this case the question arises whether the lichen planus eruption was not a reaction to the arsphenamines. Such lichen-planus-like eruptions occasionally occur.

DR. LOUIS CHARGIN: I cannot agree with Dr. Rostenberg's conception of the condition as a lichen-planus-like eruption due to arsphenamine, since continued medication with arsphenamine not only did not activate but helped to cause involution of the process.

DR. SAMUEL M. PECK: It is well to remember that before one considers the present eruption as being due to arsphenamine—in other words, a drug eruption—Milian's theory of biotropism should be mentioned. According to this theory, eruptions occurring during the administration of drugs are due to the same viruses which produce the actual exanthems, the drug acting in the role of an exciting factor. Most American observers consider the lichen-planus-like eruption in the course of arsenical therapy as an actual drug eruption.

DR. CHARLES PINES: Lichen planus not infrequently leaves pigmentation after the lesions have cleared. In the case presented, however, the pigmentation is not limited to the former sites of lichen planus but is more or less generalized. Since the patient was under treatment with arsenic for syphilis prior to and during the attack of lichen planus, it would appear likely that the arsenic is an added factor in the production of the pigmentation. Histologic observations corroborate the clinical diagnosis of lichen planus with pigmentation.

Squamous Cell Epithelioma of the Tongue. Presented by DR. THEODORE ROSENTHAL.

J. P., aged 57, born in Scotland, was first seen in August 1933, complaining of a lesion on the tip of the tongue, which had lasted about two years. He had noticed a whiteness of the tongue for about fifteen years prior to admission. He was a heavy cigaret smoker but had never smoked pipes. At about the age of 18 he had had an initial lesion on the genitals and had received local treatment at Bellevue Hospital.

Examination in 1933 showed that the dorsum of the tongue was glistening white. To the left of the median line and near the tip of the tongue there was an irregular ulceration the size of a dime, which on palpation felt hard. On the posterior portion of the left side of the tongue, opposite the left lower molars, the tongue was indurated and thickened. A small hard submental gland was palpable. On August 22 the Wassermann reaction was 2 plus and the Kahn reaction 3 plus. The patient received two injections of bismuth subsalicylate and one of neoarsphenamine. He then disappeared from observation.

He reappeared in March 1940. He had received no additional treatment during the seven year interval. There was no change in his condition. There is an indurated lesion with superficial ulceration on the left side of the tip of the tongue.

There are diffuse glistening areas on the dorsum of the tongue. On the left side of the dorsum of the midportion of the tongue is an elevated thickened yellowish plaque. The submental or cervical glands cannot be palpated.

The Wassermann reaction was 1 plus and the Kline reaction 3 plus. A portion of the lesion on the tip of the tongue was removed for histologic examination. It showed an area of ulceration and proliferation downward and nests of somewhat atypical squamous cells; many of these cells contained horny pearls. The histologic diagnosis was cornifying squamous cell epithelioma of the tongue.

DISCUSSION

DR. ADOLPH ROSTENBERG: It is of interest that the clinical aspect of the lesion was described seven years ago exactly as it appears now. It is remarkable that a squamous cell epithelioma should last for so many years without progressing.

DR. WILBERT SACHS: I cannot conceive of such a lesion being present for seven years if the pathologic changes seen tonight were the same seven years ago. The microscopic picture is that of a malignant process.

DR. DAVID L. SATENSTEIN: The section shows bands and finger-like masses of infiltrating cells extending into the cutis. In the central portion of these strands the cells are almost completely cornified. The marginal cells have lost the characteristics of the prickle cells. There are no cells breaking away from these infiltrating masses. They are surrounded by a moderate inflammatory zone. The entire picture is one of prickle cell epithelioma, which at present appears inactive.

DR. CHARLES WOLF: This lesion will respond favorably to contact roentgen ray therapy. It is a slowly growing tumor, and there are no enlarged cervical glands.

DR. CLINTON H. MARTIN: I am not in favor of roentgen ray therapy, regardless of whether the lesion advances or not. I prefer excision of the lesion, thus avoiding progress and stimulation.

DR. THEODORE ROSENTHAL: As pointed out by Dr. Rostenberg, the condition presents almost the same appearance today that it did seven years ago. Dr. Satenstein has reconciled the clinical and histologic observations by his explanation.

Atrophy of Subcutaneous Fat Due to Protamine Zinc Insulin. Presented by DR. HENRY SILVER and DR. MAX BERKOVSKY.

B. O., a woman aged 68, has had diabetes for the past three years. She has been treated with daily injections of protamine zinc insulin, and for the last seven months the injections have been administered by her husband. The sites of the injections are the upper parts of the arms. About six months ago the patient noticed a depressed area on the left arm, which was not preceded by an inflammatory reaction.

In the subdeltoid area of the left arm there is a deep depression with practically complete loss of the subcutaneous fat, measuring 3 by 2 inches (7.5 by 5 cm.). The overlying skin is normal except for slight wrinkling. The lower border of the involved area is thickened. About ½ inch (1.3 cm.) above the upper border there is another depressed area, smaller and less pronounced.

In the deltoid region of the right arm is a similar depression with absence of the subcutaneous fat. This area is not as deep as that of the left arm and may be explained by the fact that the left arm was used more frequently. The sugar content of the blood ranged from 180 to 240 mg. per hundred cubic centimeters. Sugar was present in the urine. The Wassermann reaction was negative.

The patient was instructed to inject protamine zinc insulin every other day into an outlined area on the thigh. Two weeks later a painful swelling at the site of injection developed. There was no visible redness over the area.

Tissue was removed from the depressed area of the left arm and from the area of swelling on the thigh and examined histologically by Dr. Satenstein.

Arm.—The epidermis showed no important change. The entire cutis was somewhat thin but otherwise showed no pathologic changes. Only a small amount of fat was present in the subcutaneous area. The spaces between the septums of the connective tissue were smaller than usual. There was some breaking up of these septums. There was a small amount of pigment in the fat area.

Thigh.—The epidermis showed little change. The subpapillary zone showed heavy lymphocytic infiltration around the blood vessels. In the cutis the collagen bundles were swollen. There was a small area of connective tissue on the fat zone in which were some sweat glands. The septums of the connective tissue were thin and fragmented. The cells of the sweat glands were swollen, partly vacuolated and partly granular. The picture was that of an urticarial type of reaction, i. e., dermatitis with parenchymatous swelling of the cutis.

DISCUSSION

DR. HENRY SILVER: Atrophy of subcutaneous fat following administration of insulin is rare. The usual interpretation given is that a lipase is produced in a susceptible person, with resulting dissolution of the fat. The possibility of another interpretation suggests itself, namely, that the fat necrosis might be an Arthus phenomenon.

DR. MARION B. SULZBERGER: The Arthus phenomenon is a local manifestation of hypersensitivity. It is looked on as a local anaphylaxis and is associated with precipitins, passive transference and anaphylactic antibodies. These would have to be demonstrated to prove that the reaction in this case is the equivalent of the Arthus phenomenon. This phenomenon has as yet been observed in typical form only in animals.

DR. ARTHUR SAYER: I am wondering whether the fat atrophy is not the sequel of an inflammatory process which occurs at the site of injection. It is conceivable that the area of destruction caused by the inflammation results in atrophy of the involved tissue

DR. HENRY SILVER: The histologic picture of an experimentally produced lesion was that of an urticarial reaction in the cutis with beginning atrophy of fat. The fat atrophy may be interpreted as an Arthus phenomenon. The significance of these phenomena in clinical medicine and especially in dermatology is not as yet fully appreciated. Reports which merit attention, however, are already on hand.

In diabetes a state of vulnerability of the fat tissue must be assumed. The repeated injections of the same material (insulin) cause first an inflammatory reaction, as evidenced by the urticarial reaction histologically, and later a local necrosis characteristic of the Arthus phenomenon.

A Case for Diagnosis (Lymphoblastoma?). Presented by DR. ADOLPH ROSTENBERG.

A housewife aged 58 was first seen at the Bronx Hospital on Dec. 9, 1939. She presented a generalized eruption which began eight years ago on the hands and forearms and gradually involved the entire body. Her main complaint was intolerable itching. She had been treated at various clinics. About a month ago she noticed the appearance of subcutaneous nodules on various parts of the body.

There is a generalized erythroderma with considerable infiltration of the skin and superficial scaling which is most pronounced about the neck. Scattered throughout there are about a dozen subcutaneous nodules the size of a pea or cherry. An unusual feature is frequent profuse sweating of the neck and chest.

Complete physical examination including roentgen ray studies gave negative results. The urine and stool were normal. The Wassermann and Kahn reactions were negative. The chemical examination of the blood gave negative results. Examination of the blood showed 84 per cent hemoglobin and 4,500,000 erythro-

cytes and 7,400 leukocytes per cubic millimeter, with 53 per cent polymorphonuclear leukocytes, 11 per cent eosinophils, 1 per cent band forms, 22 per cent lymphocytes and 13 per cent monocytes.

Puncture of the sternal bone revealed no evidence of leukemic infiltration of the bone marrow. There was a definite reduction in the number of leukocytes. Many red blood cells and megakaryocytes were present.

The histologic examination showed no changes of the epidermis. The subcutaneous tissue was the seat of irregular interlacing groups of spindle cells in a rather delicate collagenous stroma. Many of the spindle cells had large hyperchromatic nuclei.

Since the patient has left the hospital the condition has changed greatly. The erythroderma and the cutaneous infiltration have diminished considerably except on the neck and upper extremities, where the former process is still in evidence. The nodules have disappeared spontaneously but reappeared in different regions at various times.

DISCUSSION

DR. CHARLES PINES: This patient has been under observation at the clinic of the Bellevue Hospital for about six years. The diagnosis on admission was seborrheic eczema. The condition yielded to treatment readily at the outset. The eruption recurred, and it was necessary to hospitalize the patient. At that time there appeared tender and painful subcutaneous nodules, which on histologic examination were reported as neurofibromas. The blood picture was normal on several occasions, and at no time was there any suspicion of lymphoblastoma.

DR. ADOLPH ROSTENBERG: There are some elements in this case that point to the diagnosis of lymphoblastoma, possibly mycosis fungoides. The cutaneous picture changed from time to time, depending on the degree of erythroderma and the infiltration of the skin. The itching, however, always remained intense. It is difficult to reconcile a diagnosis of neurofibromatosis with the picture in this case, since in that condition the tumors do not come and go.

Eczema Venenatum (Dye in Clothing). Presented by DR. MARION B. SULZBERGER.

S. G., a moving picture manager aged 58, a patient at the Montefiore Hospital for Chronic Diseases, presents a generalized, highly pruritic, scaling, erythematous dermatitis of long standing. His father had asthma, and a younger brother had hay fever. He never has had hives but says that he has felt slight itching after eating strawberries. The present disease lasted sixteen months and began between the toes in October 1938. It soon became generalized. The patient was treated by his physician and was hospitalized at the New York Post-Graduate Medical School and Hospital, the Morrisania City Hospital and the Montefiore Hospital for Chronic Diseases.

The local condition, of which only remnants are now seen, was characterized by generalized itching, redness and some follicular swellings and hyperkeratoses. Recurrences were frequent and always occurred when the patient left the hospital, whether he went home or not. Patch tests revealed severe sensitivity to the lining of one of his suits, and to paraphenylenediamine and slight sensitivity to other linings and even to white shirts. The washings used to rinse the offending lining gave strongly positive reactions (eighteen washings). During the last two weeks a fluctuation in the degree of sensitivity seems to have taken place, as demonstrated by much weaker reactions to the offending allergens. The clothing eliciting strongly positive reactions when used in patch tests was eliminated, and the patient was allowed to wear only clothing (including shirts and linens) which had produced no reaction in cutaneous tests. Since instituting this change of apparel (over three weeks), he has returned home several times without suffering exacerbations of the dermatosis.

DISCUSSION

DR. CHARLES GREENHOUSE: This man was under my care some time in February 1939, after he had been treated by another dermatologist. The clinical aspect was that of dermatophytosis of the toes and dermatophytid of the lower extremities. The eruption did not respond to treatment satisfactorily. The patient left me and was treated by another dermatologist, who made the same diagnosis. The eruption became generalized, and he returned to me for treatment. At this time the condition resembled the eruption described by Sulzberger and Garbe as chronic lichenoid and discoid dermatitis. It is not common to find that patients presenting this clinical picture are sensitive to dyes or other external irritants, and therefore I do not feel that clothing dyes are primarily responsible for this condition. However, I should like to commend Dr. Sulzberger on the improvement this man has shown thus far.

DR. MARION B. SULZBERGER: The patient had an erythematous, desquamating and lichenoid papular eruption over almost the entire body. The important features of the case are (1) the fact that the effect of environmental change may be due to the difference in the particular clothing worn in different environments, (2) the extreme degree of this patient's hypersensitivity to dyed material, there being enough dye present in the water of the twelfth rinsing to produce reactions, and even after eighteen washings the material itself when applied as patch tests produced infiltrated lesions persisting for weeks, (3) the fluctuations, i. e., the reduction in sensitivity which has occurred in this case, which may be due to spontaneous fluctuation, to the effect of repeated patch tests with the allergen or to the effect of hospitalization and clearing up of the dermatosis. This man was so sensitive that any clothing which was washed in the same tub as dyed materials, even though it was itself white, still produced a reaction.

Dr. Kadisch's careful and extensive tests performed during the last months have shown the patient to be sensitive to numerous aniline dyes but not to dyes of the alizarin series.

NOTE.—The patient is now, one month later, entirely well. The skin remains clear as long as he wears white clothing.

Erythrose Peribuccale Pigmentaire (Brocq). Presented by DR. MAURICE UMANSKY.

E. B., a girl aged 16, came to the clinic of the Lebanon Hospital presenting an eruption of ten months' duration. The involved areas are the chin, the nasolabial folds and the nose. There is a definitely outlined reddish brown discoloration present. The intensity of the redness varies from day to day. On pressure with the diascope the redness disappears and yellowish brown pigmentation remains. There is no evidence of scaling or infiltration. The girl is otherwise in good health. Her menstrual cycle began when she was 13½, and her periods are regular.

DISCUSSION

DR. ARTHUR SAYER: It is my belief that the eruption is seborrheic eczema rather than érythrose peribuccale pigmentaire, because of the greasy appearance. Also, in érythrose peribuccale pigmentaire the eruption is symmetric and usually more extensive.

DR. MAURICE UMANSKY: In the majority of the recorded cases the condition has been observed in women in their thirties. There are several factors which favor this diagnosis. These are: the sharp demarcation of the lesion, the absence of scaling, the fluctuation in the intensity of the erythema (which is probably due to the fact that the vessels in the skin are dilated to a greater or lesser degree at various times) and the resistence to treatment.

Patch tests with cosmetics which the patient used (powder, rouge, lipstick and cold cream) gave negative reactions. A photosensitization reaction was seen from application of perfume and subsequent exposure to ultraviolet rays.

Many of the examples of érythrose peribuccale pigmentaire that have been described occurred in seborrheic subjects, in women who had oily skin and patulous orifices of the ducts of the sebaceous glands. This fact makes one think of seborrheic dermatitis. But the elements of this type of dermatitis are missing in the patient presented. Discoloration and redness which disappear on diascopic pressure are the only visible changes in the skin.

Melanodermatitis. Presented by DR. MARION B. SULZBERGER.

J. S., a factory worker aged 42, a patient of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, presents a brownish discoloration, which began about eight months ago on the extensor aspect of the right forearm. Since then the involved area has grown. Otherwise the lesion has remained the same. There are no subjective symptoms.

The patient states that machine oil is sprayed every day on the right forearm during the first few minutes of the working day. The machine which he operates is oiled every morning before work is started.

The area involved is fairly sharply circumscribed, the size of two palms and situated on the extensor surface of the right forearm. There are diffuse dark brown discoloration with exaggerated cutaneous markings and some mottled depigmentation together with numerous follicular keratoses. The patient eats a normal diet.

A Case for Diagnosis (Squamous Cell Epithelioma of the Tongue? Fungating Iodide Eruption of the Tongue?). Presented by DR. MARION B. SULZBERGER.

S. M., a man aged 62, was presented before this society in February 1940 (ARCH. DERMAT. & SYPH. **42**:528 [Sept.] 1940). The patient died, and an autopsy was performed. Another rapidly growing lesion had developed on the mucous membrane of the mouth about a week before he died. This lesion was fungating and ulcerated. It was excised and showed the typical picture of an isolated metastasis, i. e., a circumscribed group of foreign cells in the cutis. The nodule was discrete and was embedded in the normal tissue in the cutis, somewhat below the epithelial margin. At autopsy there were nodules the size of a bean in the right side of the cerebellum and several nodules the size of a pea and larger in the spleen. There were also minute nodules in the left side of the heart among the trabeculae carneae. The lungs were grossly normal. There was a sanguinous, necrotic tumor the size of a grapefruit adjacent to the right kidney. The histologic study of the tumor revealed an adenocarcinoma.

DISCUSSION

DR. WILBERT SACHS: The pathologic picture of the metastatic lesion on the gum is the same as that of the lesions on the tongue. In all three lesions the cells are of the anaplastic variety. There are none of the features in these cells that one finds in hypernephromas. In metastatic hypernephroma of the skin the pathologic changes are different from those found in this case.

Book Reviews

The Emperor's Itch. By Reuben Friedman, M.D. Price $1.50. Pp. 82. New York: Froben Press, Inc., 1940.

The author of this monograph has gathered together the pros and cons as to whether Napoleon's cutaneous disease was scabies, and in his summation he presents evidence which he believes is sufficiently convincing to throw doubt on that diagnosis. He suggests the possibility that the emperor's dermatosis was dermatitis herpetiformis or even neurotic excoriations. The book is copiously annotated and the subject most interestingly presented. With Dr. Friedman's well known interest in the historical side of scabies, this could not well be otherwise.

The reviewer, however, does not believe that the evidence submitted by the author is sufficiently conclusive to corroborate definitely the diagnosis of dermatitis herpetiformis or eliminate that of scabies. Out of the welter of contradictory statements from Napoleonic contemporaries, both medical and lay, one fact remains clear, and that is that Napoleon for many years did have a cutaneous disease, the nature of which can only approximately be determined by analysis and deduction. The known facts in favor of scabies are: The incessant wars following the French Revolution caused an enormous increase in that disease in the armies of France. Even the citizens of Paris were greatly affected, as proved by the fact that by the end of the eighteenth century L'Hôpital Saint-Louis had eleven hundred beds, seven hundred of which were reserved for patients with scabies.

That Napoleon could have contracted the disease at Toulon, France, by means of the proverbial rammer of a cannon from the hands of a dead gunner infected with scabies is possible but by no means probable; but what is probable is the fact that he frequently mixed freely with his troops, in camps, on battle fields and in hospitals and could therefore not only be easily infected but also reinfected. At that time scabies was most indifferently treated, and scientific dermatology was practically unknown. During the Napoleonic era sulfur ointment was applied only to the hands, wrists and feet. In fact, it was not until 1847 that Bazin revolutionized the treatment of scabies by the universal application of sulfur ointment, thereby ridding the wards of L'Hôpital Saint-Louis of patients with chronic scabies. Sulfur baths as used in Napoleon's time were not, in the reviewer's opinion, a therapeutic test. Biett as early as 1814 installed at L'Hôpital Saint-Louis twenty-four copper bath tubs for the treatment of scabies. By 1818 a hundred and thirty thousand baths a year were given; yet the incidence of scabies at that hospital was as great as ever. According to the author, Napoleon was extremely solicitious in reference to the patients with scabies in his army and wished to establish hospitals for its treatment. Could this solicitation be ascribed to painful personal experience? In view of the indifferent treatment this disease received, it is not improbable that, despite Napoleon's known irreproachably cleanly habits, he could have had scabies for several years and even, as the author suggests, secondary itching and eczematoid, pyodermic skin.

The author quotes both Gachoti and Sokoloff's statement that Marie Louise, Napoleon's second wife, had scabies, but he is convinced that she did not get the disease from Napoleon but received her infection from some other source.

The points marshalled against the diagnosis of scabies are: the long duration of the Emperor's cutaneous disease, the fact that neither Josephine nor her children became infected, the appearance on his face at one time of excoriated lesions and the fact that Antommarchi personally saw Napoleon at St. Helena excoriating and tearing at the skin of his thighs, suggesting the diagnosis of neurotic excoriations.

This reviewer agrees entirely with the author in ascribing Napoleon's chronic cough, pallor, emaciation and weakness in his early years to tuberculosis; this is

further corroborated by the autopsy observations of Antommarchi in St. Helena, who stated that the upper lobe of the left lung contained several tuberculous excavations. From 1787 to 1789 Napoleon himself stated that he had had severe attacks of malarial fever. The course of his last illness and the observations at autopsy by Dr. Archibald Arnott, surgeon of the twentieth regiment, the only British surgeon present, and by Dr. Antommarchi, Napoleon's personal physician, clearly describe the symptoms of gastric cancer and the pathologic changes of a perforating cancer of the stomach.

The author is entirely correct in ascribing Napoleon's characteristic pose to a mannerism, which probably began at adolescence. It is dermatologically inconceivable that a dermatosis could cause a localized pruritus for thirty or more years. This reviewer is of the opinion that artists are more responsible for the popularization of the pose than Napoleon himself and that he made much less use of it than is indicated in his portraits.

Séro-diagnostic de la syphilis: Etudes comparatives de la sensibilité et de la specifici de différentes réactions actuellement employées. By T. M. Vogelsang. Pp. 217. Bergen: J. W. Eides Boktrykkeri, 1940.

This book is a study of the serologic tests of the blood and spinal fluid performed in the Central Laboratory of the western part of Norway. The period of study was from June 1935 to August 1939. To that laboratory are sent the blood and spinal fluid of patients in many institutions.

The author discusses in detail the flocculation and complement fixation tests. The flocculation tests employed were: the standard Kahn test, the Kahn microscopic test, the Meinicke clarification test, the Meinicke microscopic test, the two modifications of the Müller test, the Kline diagnostic and exclusion tests, the Eagle test, the Rytz test and the Chediack test. Some of these are little used in America. The technic and reagents required for the performance of each test are explained in detail.

The results obtained with these tests are given in the text and in eighty-nine tables and eleven diagrams. The bibliography consists of two hundred and forty-seven references, mostly to European authors.

The only criticism is that too much space is dedicated to the technical part of the tests and too little to the interpretation of results.

The book should prove of value to those interested in serology.